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THE WESTERN Journal of Medicine

VOLUME 121 • NUMBER 1 **JULY 1974**

1 *Neurological Manifestations of Acute Granulocytic Leukemia*
S. A. ARMENTROUT, MD, and R. F. ULRICH, MD

6 *Non-Invasive Colonoscopic Polypectomy—Review of 100 Cases*
JOEL F. PANISH, MD, and GEORGE BERCI, MD

10 *The Spectrum of Asbestos-Related Diseases*
WILLIAM N. ROM, MD, MPH, and PHILIP E. S. PALMER, FRCP (Edin), FFR

MEDICAL PROGRESS

22 *Metabolism and Action of the Hormone Vitamin D—Its Relation to Diseases of Calcium Homeostasis* JACK W. COBURN, MD, DAVID L. HARTENBOWER, MD, and ANTHONY W. NORMAN, PhD

SPECIALTY CONFERENCE

45 *Inappropriate Secretion of Antidiuretic Hormone*
Participants: STANLEY A. MENDOZA, MD, and MARGARET KELLER, MD
Pediatric Grand Rounds, University Hospital of San Diego County, and University of California San Diego, School of Medicine

MEDICAL STAFF CONFERENCE

50 *Complications of Vomiting—The Boerhaave and the Mallory-Weiss Syndromes*
Discussion by H. DAVID WATTS, MD

55 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Allergy*

62 EDITORIALS • *Adversaries in Patient Care* • *"Inappropriate" Versus "Appropriate" Antidiuretic Hormone Secretion* • *The Impact of Recent Findings Concerning Vitamin D Metabolism on Clinical Medicine* • *Top Flight Brains for Medicine*

CASE REPORTS

66 *Vibrio Parahaemolyticus Gastroenteritis from Eating Conchs*
FRANK S. RHAME, MD, and S. BENSON WERNER, MD

69 LETTERS TO THE EDITOR

TRAUMA ROUNDS

71 *Management of Ruptured Aneurysms of the Abdominal Aorta*
Chief Discussant: EDWIN J. WYLIE, MD

MEDICAL OPINION

77 *The Myth of Sickle Cell Trait* LONNIE R. BRISTOW, MD

GOVERNMENT AND MEDICINE

83 *Medi-Cal—Another Way* JAMES G. RONEY, JR., MD, PhD, MPH

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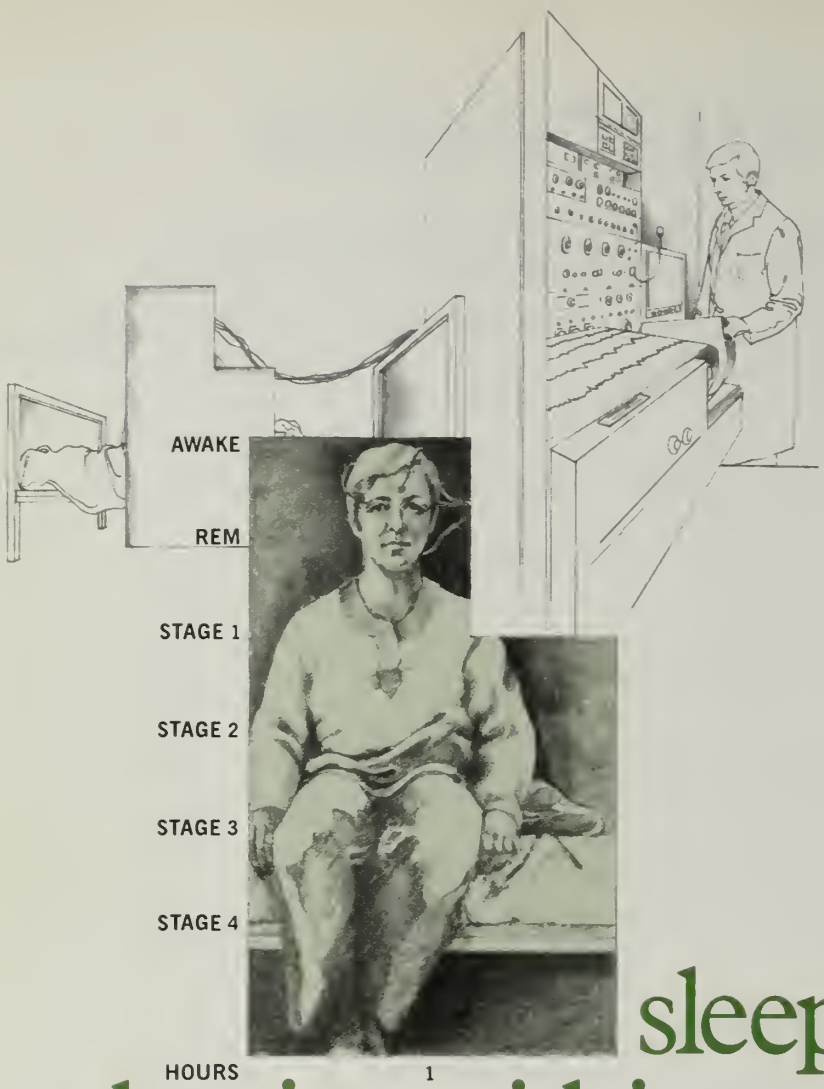

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an initial benefit of

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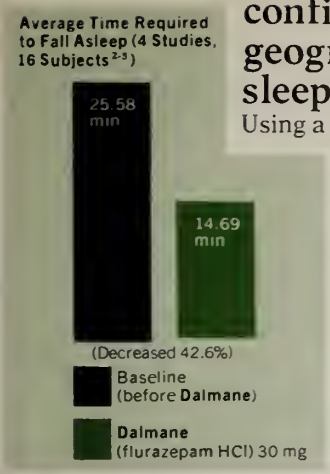
proved by a 22-night clinical study of insomnia patients in the sleep research laboratory and at home[1]

Three insomnia patients selected for difficulty falling asleep were administered Dalmane (flurazepam HCl) 30 mg for 14 consecutive nights. Placebo was given for four nights prior to and four nights after Dalmane. Physiologic tracings on Dalmane nights 1-3 showed sleep induction time averaged 13.90 minutes; on Dalmane nights 12-14, 18.80 minutes. Combined average for the 6 monitored drug nights was 16.35 minutes.[1]



confirmed by clinical studies in four geographically separated sleep research laboratories[2-5]

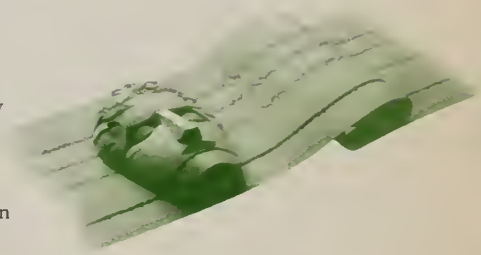
Using a 14-night protocol involving eight insomniac and eight normal subjects, four studies confirmed the sleep-inducing effectiveness of Dalmane (flurazepam HCl) and the reproducibility of this response. On average, one 30-mg capsule induced sleep within 17 minutes. In all these studies, Dalmane induced sleep rapidly, reduced nighttime awakenings, and provided 7 to 8 hours of sleep without repeating dosage.[2-5]

Dalmane (flurazepam HCl) induces and maintains sleep, with relative safety

Dalmane is generally well tolerated; morning "hang-over" has been relatively infrequent. While dizziness, drowsiness, lightheadedness and the like have been noted most often, particularly in the elderly and debilitated, physicians should be aware of the possibility of more serious reactions, as noted below.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.
Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.



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One 15-mg capsule *h.s.* — initial dosage for elderly or debilitated patients.

- **induces sleep within 17 minutes, on average**
- **reduces nighttime awakenings**
- **sustains sleep 7 to 8 hours, on average, without repeating dosage**

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5. Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ

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Case history #4

Charles' well-being comes first.

Charles' being well comes first.

In September 1968, while working as a driver/salesman for a Sacramento beverage company, Charles Foster's automobile overturned. He was thrown from the car and sustained a number of serious injuries, including a compression fracture of the vertebrae with cord injury, making him paraplegic.

During Charles' initial period of intensive care, State Fund cooperated with his doctors, setting up a long-range program of health care. Charles suffered a cardiac arrest during spinal surgery, but he was successfully resuscitated and continued to improve. After leaving the hospital, he entered the Kaiser Foundation Rehabilitation Center in Vallejo, where he quickly learned to adapt to his paralysis.

State Fund's rehabilitation staff visited Charles regularly to help him plan his new life. They helped him buy a specially equipped car to drive to and from school and arranged and paid for home alterations to accommodate his wheelchair and his impairment.

In 1973, Charles Foster took advantage of State Fund's *Therapeutic Capitalization* Program, enabling him to receive a lump-sum payment for the total projected cost of his lifetime medical and living expenses, which he invested in secure mutual funds and in a business of his own. Today, Charles is teamed with another paraplegic, and together they operate The Wheelchair Boutique, specializing in sales, repair, and rental of hospital equipment.

Charles has come a long way since his accident, with courage and determination—and the help of State Fund.

Conserving your human resources is our only business

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Must vasodilators and therapy for other diseases come into conflict?

not if the vasodilator is

VASODILAN®

(ISOXSUPRINE HCl)

the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

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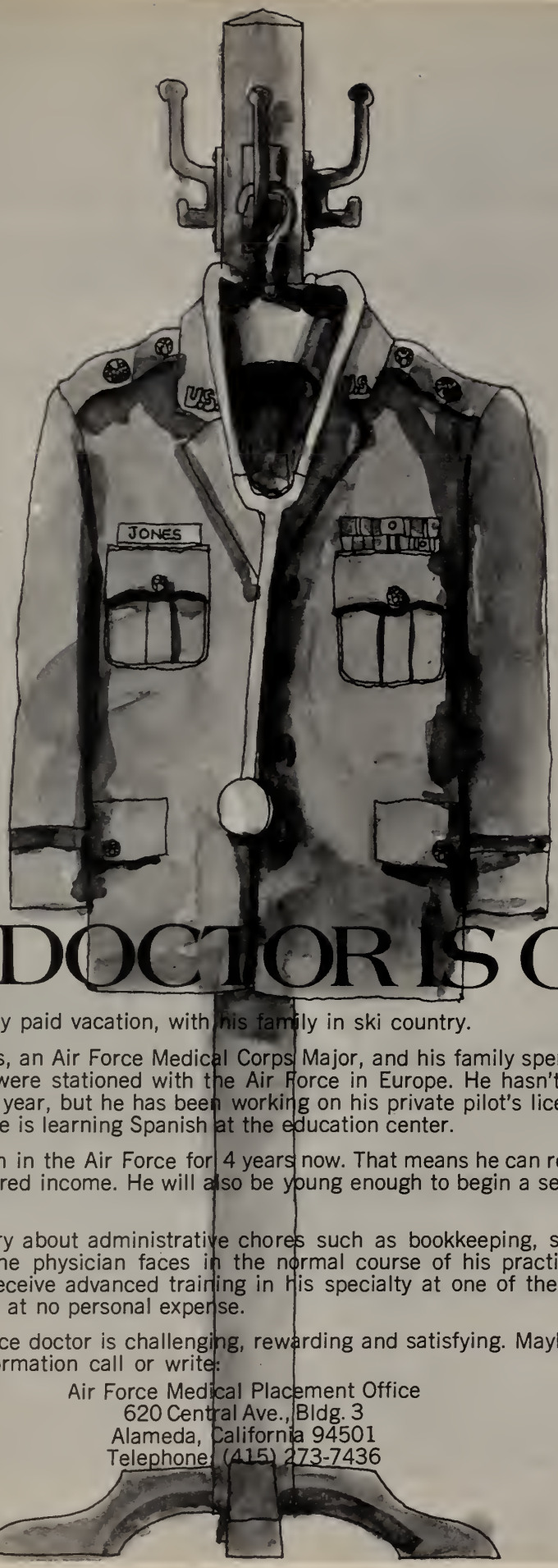

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He's enjoying a 30 day paid vacation, with his family in ski country.

Last year Doctor Jones, an Air Force Medical Corps Major, and his family spent their vacation in Switzerland. They were stationed with the Air Force in Europe. He hasn't said what they have planned for next year, but he has been working on his private pilot's license at the base flying club and his wife is learning Spanish at the education center.

Doctor Jones has been in the Air Force for 4 years now. That means he can retire in less than 16 years with an assured income. He will also be young enough to begin a second successful career.

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Provides the therapeutic effectiveness of divided daily doses with no loss of safety.

*Each capsule contains imipramine pamoate equivalent to 150, 125, 100 or 75 mg. of imipramine hydrochloride.

One dose lasts from bedtime to bedtime.

For single-dose therapy in depression when the dosage is established.

- for many patients, the 150-mg. capsule may be the most effective single daily dose.
- may markedly reduce the probability of missed doses.
- offers dosage convenience that assures greater patient cooperation.
- becomes part of the regular bedtime routine—making it easier to establish a more reliable pattern of self-medication.
- offers the therapeutic equivalency of divided daily doses of Tofranil®, imipramine hydrochloride, with no loss of efficacy or safety.
- has the convenience and flexibility of a full range of single daily dosage strengths.
- saves time and cost of dosage administration in the hospital.

Please read the prescribing information for details of usage, precautions, warnings, contraindications, adverse experiences, and dosage recommendations. A summary appears on the following page.

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imipramine pamoate

Capsules* of 150, 125, 100 and 75 mg.

*Each capsule contains imipramine pamoate equivalent to 150, 125, 100 or 75 mg. of imipramine hydrochloride.

One dose lasts from bedtime to bedtime.

Tofranil-PM®
brand of imipramine pamoate
Tofranil®
brand of imipramine hydrochloride USP

Indications: For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states

Contraindications: The concomitant use of monoamine oxidase inhibiting compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur in patients receiving such combinations. The potentiation of adverse effects can be serious, or even fatal When it is desired to substitute Tofranil, brand of imipramine hydrochloride, in patients receiving a monoamine oxidase inhibitor, as long an interval should elapse as the clinical situation will allow, with a minimum of 14 days. Initial dosage should be low and increases should be gradual and cautiously prescribed The drug is contraindicated during the acute recovery period after a myocardial infarction. Patients with a known hypersensitivity to this compound should not be given the drug The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind

Warnings: *Usage in Pregnancy:* Safe use of imipramine during pregnancy and lactation has not been established; therefore, in administering the drug to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards Animal reproduction studies have yielded inconclusive results. There have been clinical reports of congenital malformation associated with the use of this drug, but a causal relationship has not been confirmed.

Extreme caution should be used when this drug is given to:

- patients with cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes and tachycardia.
- patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties;
- hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity;
- patients with a history of seizure disorder because this drug has been shown to lower the seizure threshold,
- patients receiving guanethidine or similar agents since imipramine may block the pharmacologic effects of these drugs.

Usage in Children: Pending evaluation of results from clinical trials in children, Tofranil, brand of imipramine hydrochloride, is not recommended for treatment of depression in patients under twelve years of age.

Tofranil-PM, brand of imipramine pamoate, should not be used in children of any age because of the increased potential for acute overdosage due to the high unit potency (75 mg., 100 mg., 125 mg. and 150 mg.). Each capsule contains imipramine pamoate equivalent to 75 mg., 100 mg., 125 mg. or 150 mg. imipramine hydrochloride.

Since imipramine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

Precautions: It should be kept in mind that the possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs Such patients should be carefully supervised during the early phase of treatment with Tofranil, brand of imipramine hydrochloride, and may require hospitalization. Prescriptions should be written for the smallest amount feasible.

Hypomanic or manic episodes may occur, particularly in patients with cyclic disorders Such reactions may necessitate discontinuation of the drug. If needed, Tofranil, brand of imipramine hydrochloride, may be resumed in lower dosage when these episodes are relieved Administration of a tranquilizer may be useful in controlling such episodes

Prior to elective surgery, imipramine hydrochloride should be discontinued for as long as the clinical situation will allow.

An activation of the psychosis may occasionally be observed in schizophrenic patients and may require reduction of dosage and the addition of a phenothiazine

In occasional susceptible patients or in those receiving anticholinergic drugs (including antiparkinsonism agents) in addition, the atropine-like effects may become more pronounced (e.g., paralytic ileus). Close supervision and careful adjustment of dosage is required when this drug is administered concomitantly with anticholinergic or sympathomimetic drugs.

Avoid the use of preparations, such as decongestants and local anesthetics, which contain any sympathomimetic amine (e.g., adrenalin, noradrenalin), since it has been reported that tricyclic antidepressants can potentiate the effects of catecholamines

Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggerated effects.

Both elevation and lowering of blood sugar levels have been reported

Concurrent administration of imipramine with electroshock therapy may increase the hazards; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Adverse Reactions: Note: Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when imipramine is administered.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke, falls

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurological: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus

Anticholinergic: Dry mouth, and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis; constipation, paralytic ileus, urinary retention, delayed micturition, dilation of the urinary tract

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue); drug fever; cross-sensitivity with desipramine.

Hematologic: Bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathological neutrophil depression.

Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue

Endocrine: Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling, elevation or depression of blood sugar levels

Other: Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing, urinary frequency; drowsiness, dizziness, weakness and fatigue; headache; parotid swelling; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise

Dosage and Administration: Lower dosages are recommended for elderly patients and adolescents Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. Dosage should be initiated with Tofranil, brand of imipramine hydrochloride, at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission.

Once-a-day maintenance dosage can be provided with Tofranil-PM, brand of imipramine pamoate, capsules if this dosage has been established as explained above. This dose may be given at bedtime. For the occasional patient who manifests stimulation and insomnia with this dosage regimen, the capsules may be given in the morning.

Parenteral administration should be used only for starting therapy in patients unable or unwilling to use oral medication The oral form should supplant the injectable as soon as possible.

How Supplied: Tofranil, brand of imipramine hydrochloride: Round tablets of 25 and 50 mg., triangular tablets of 10 mg.; and ampuls, each containing 25 mg in 2 cc. for I.M. administration.

Tofranil-PM, brand of imipramine pamoate: Capsules of 75, 100, 125 and 150 mg. (Each capsule contains imipramine pamoate equivalent to 75, 100, 125 or 150 mg. of imipramine hydrochloride.) (B) 98-146-850-P (2/74)

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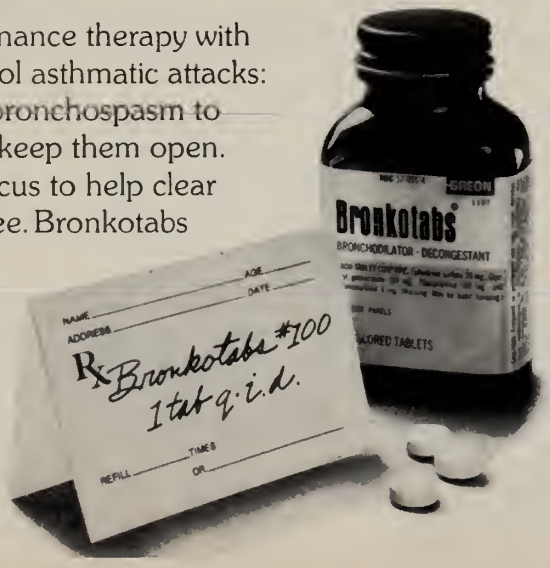

PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

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fore prescribing, see complete prescribing ormation in SK&F literature or *PDR*. The lowing is a brief summary.

lications: Edema associated with congestive ırt failure, cirrhosis of the liver, the nephrotic ıdrome; steroid-induced and idiopathic :ma; edema resistant to other diuretic therapy. so, mild to moderate hypertension.

ntraindications: Pre-existing elevated serum :assium. Hypersensitivity to either com- nent. Continued use in progressive renal or patic dysfunction or developing hyperkalemia.

ırnings: Do not use dietary potassium supple- nts or potassium salts unless hypokalemia velops or dietary potassium intake is markedly paired. Enteric-coated potassium salts may ıse small bowel stenosis with or without eration. Hyperkalemia (>5.4 mEq/L) has en reported in 4% of patients under 60 years, 12% of patients over 60 years, and in less ın 8% of patients overall. Rarely, cases have en associated with cardiac irregularities. cordingly, check serum potassium during rapy, particularly in patients with suspected confirmed renal insufficiency (e.g., elderly or ıbetics). If hyperkalemia develops, substitute hiazide alone. If spironolactone is used ıcomitantly with 'Dyazide', check serum tassium frequently—both can cause potassium ention and sometimes hyperkalemia. Two aths have been reported in patients on such nbined therapy (in one, recommended sage was exceeded; in the other, serum elec- lytes were not properly monitored). Observe tients on 'Dyazide' regularly for possible ood dyscrasias, liver damage or other idio- ıcratic reactions. Blood dyscrasias have been orted in patients receiving Dyrenium iamterene, SK&F). Rarely, leukopenia, ombocytopenia, agranulocytosis, and aplastic emia have been reported with the thiazides. ıtch for signs of impending coma in acutely cirrhotics. Thiazides are reported to cross the ıcental barrier and appear in breast milk. is may result in fetal or neonatal hyperbili- binemia, thrombocytopenia, altered carbo- drate metabolism and possibly other adverse ıctions that have occurred in the adult. When ed during pregnancy or in women who might ar children, weigh potential benefits against ssible hazards to fetus.

ecautions: Do periodic serum electrolyte and JN determinations. Do periodic hematologic ıdies in cirrhotics with splenomegaly. Anti- pertensive effects may be enhanced in post- npathectomy patients. The following may cur: hyperuricemia and gout, reversible rogen retention, decreasing alkali reserve h possible metabolic acidosis, hyperglycemia d glycosuria (diabetic insulin requirements ıy be altered), digitalis intoxication (in pokalemia). Use cautiously in surgical tients. Concomitant use with antihypertensive ents may result in an additive hypotensive ect.

lverse Reactions: Muscle cramps, weakness, ziness, headache, dry mouth; anaphylaxis; sh, urticaria, photosensitivity, purpura, other rmatological conditions; nausea and vomiting ay indicate electrolyte imbalance), diarrhea, nstipation, other gastrointestinal distur- nces. Rarely, necrotizing vasculitis, pares- esias, icterus, pancreatitis, and xanthopsia ve occurred with thiazides alone.

pplied: Bottles and Single Unit Packages of 0 capsules.

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ıbsidiary of SmithKline Corporation

rum Potassium Level Drops During Long-Term ercise, *Medical Tribune*, July 4, 1973.
implication that 'Dyazide' is useful in eventing K^+ loss in athletes is intended.

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Opinion & Dialogue

Is there a need for a drug compendium?

Government Health Official

Henry E. Simmons, M.D.
Deputy Assistant Secretary for Health
Department of Health, Education and Welfare

A drug compend of the type I envisi would fill a definite need for the prac ing physician. Su compendium wo give him all t information n essary for us a drug intelligently, and it woulc do so in a clear, concise, convenient, objective and balanced fashion.

What a Compendium Should Contain

I believe the compendium should inform the doctor what a drug will do, when he should us for what type of patient, for how long, in what dose, what benefit his patient is likely to obtain, the risks involved, and cross-reactic with other drugs.

The information would be based on the package insert anc have the same legal status. In fa a complete compendium with cc plete and current information might even eliminate the necess

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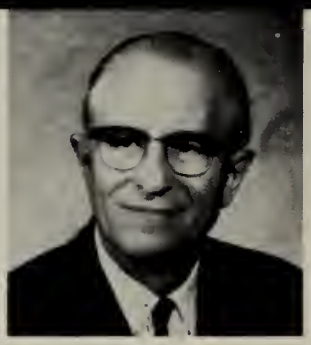

A drug compendium, or preferably compendia, should, I believe, be private, not federal, i sponsorship. They should contai comprehensive listings of drugs available for prescribing. They should be single, legibly printed volumes of reasonable size, updated quarterly or semiannually and completely revised every ye

Function of a Compendium

A compendium should furnish the following information or drugs in the following order: indi tions for use, side effects, adver drug reactions, contraindication drug interactions, drug dosage a the dosage forms marketed. Dru prices should not be included be cause they vary so widely and change rapidly.

No compendium should se forth drugs of choice or discuss relative efficacy. Such questions must be left for the practicing ph sician to decide, whether on the basis of the medical literature, h own clinical experience, advice c colleagues, information supplied by manufacturers, and so on.

Nor should a compendium undertake to educate the doctor how to use drugs. Rather, it mus be a reference source designed p marily to refresh his memory as drugs he may not use regularly. I

package insert in many in-
ces. This would constitute a
tantial saving for the manu-
rer.

By a complete compendium,
not mean a volume of prohibi-
size. You don't need a book
ribing 25,000 products with
normous amount of repetition.
er, drugs should be arranged
lass. Mutually applicable infor-
on would be provided, along
brief discussions pinpointing
rences in specific drugs of
class. Listings would be cross-
xed in a useful way.

**r Available Documents as
ces of Information**

Existing references such as
and the AMA Drug Evaluation
bviously useful but they are
mplete. Either they are not
s-referenced by generic name
do not group drugs with simi-
haracteristics, or they do not
ll the available and legally
keted drugs. And some of
e omitted may be very useful.

On the other hand, drugs made by more than one supplier, tetracycline for example, may be fully described a dozen times in the same book.

While perhaps PDR could be rearranged and cross-indexed with generics included, and while the AMA Drug Evaluation might also be modified and expanded, I am not sure that the end result would have all the attributes required for a useful compendium. At the same time, you would run the risk of amassing a voluminous and unwieldy tome.

Should Editorial Comments Accompany the Listings?

Subjective judgments, in my opinion, have no place in a compendium. However, if there is substantial evidence based on a sound body of science concerning relative efficacy of several drugs, certainly that information should be included. The committee of experts compiling and editing a particular section would also have to assess and indicate instances where a meaningful difference between drugs is pertinent.

Sponsorship, Compilation and Editing

Producing a book like this would undoubtedly be difficult and demanding. It would obviously take a great deal of talent and expertise, and would require a varied and experienced group, ranging from writers and editors to highly skilled clinicians and pharmacologists. Style, format and clarity of language would play an important part in determining the usefulness of the book. And it should be updated periodically and completely revised annually.

I have no opinion whether the government or the private sector should sponsor and/or finance the compendium. What is most important is that the compendium be an authoritative, objective and useful source of information for the doctor to have at hand as a ready reference.

---

ld in no way imply control over
practitioner's prerogatives.

Another Compendium?

A practicable, single-volume
pendium cannot, nor is it
ssary to, include all drugs on
market today. From my prac-
of internal medicine for some
ears, my experience as a con-
nt, and as a faculty member
ur or five medical schools, I
ld estimate that a doctor uses
30 to 35 drugs regularly. The
2 Physicians' Desk Reference,
dentally, contained about
0 entries.

As to whether there should be
deral compendium, in my opin-
as stated earlier, the answer is
—there should *not* be one. The
osal assumes that existing
pendia are inadequate. We're
sure of that at all. Whatever its
erfections, the present drug
rmation system in the U.S. is
, multifaceted, pluralistic and
nsive. Good compendia exist,
ell as other ample sources on
g therapy, ranging from journal
ature through AMA Drug Evalu-
n to company materials. Not
hysicians may use such
rces as often or as well as they
ld, but that is the fault of the
, not of the sources.

In any event, rather than produce another book, it makes much more sense to work on improving existing compendia, and perhaps they could, as knowledge advances, include more accumulated clinical data and experience, and more information on drug interactions and adverse reactions.

Implications of a Federal Compendium

Take a hard look at the implications of a federal compendium. It would have the force of law, virtually dictating what drugs to use and how to use them. In effect, it would be a regulatory document with legal or quasi-legal status, posing medical/legal problems similar to those the doctor may now encounter if and when he departs from the provisions of the package insert. A compendium under federal aegis would tend to restrict decisions on drug therapy to one orthodox level—a most dangerous trend for medicine.

New Compendium—A Medical Option

I detect no ground swell of initiative or support whatsoever for a federal compendium—or, for that matter, for a new compendium of any type. A 1969 PMA survey conducted by Opinion Research Corporation found that only 15 per cent of those physicians interviewed felt a new compendium was needed. And a large majority did not favor the involvement of the federal government if one were to be created, preferring instead a nongovernmental consortium.

Even if we come to a time when the medical profession itself opts for a new kind of compendium, it should be handled and financed, ideally, outside both government and industry. Final review and editorial authority could be delegated, say, to specialty bodies and medical societies—but above all, *not* the government.

Surely the health care system in the United States has far more vital matters to consider than the extensive cost and effort that would have to go into the preparation and maintenance of a new, monolithic compendium, and especially one bearing the imprimatur of the federal government.

Opinion & Dialogue

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Neurological Manifestations of Acute Granulocytic Leukemia

S. A. ARMENTROUT, MD, *Irvine, and* R. F. ULRICH, MD, *Cleveland*

Of 17 consecutive patients with acute granulocytic leukemia, all of whom were treated with cytosine arabinoside, eight had neurological complications during some stage of their disease. This high occurrence of neurological findings represents a significant increase compared with the authors' experience and, in general, with that cited in the literature. The neurological findings were usually related to significant morbidity and to mortality. Early recognition of neurological problems depends mainly upon clinical and cerebrospinal fluid findings. Progression of neurological manifestations, which can be satisfactorily treated with radiotherapy or neurosurgical methods, may result in unnecessary morbidity and premature death.

NEUROLOGICAL MANIFESTATIONS secondary to leukemia were first described by Burns[1] in 1823. Since that time many neurological manifestations have been described.[2,3] Because acute lymphocytic leukemia, which largely affects children, has a high incidence of neurological problems, the pediatric age group is often involved.[4,5] Acute granulocytic leukemia treated with the newer antimetabolites appears to be associated with a similar high incidence of neurological disease. The life span of many of the patients in the present study has been increased, and associated with this has been an increased frequency of neurological problems. While generally 10 to 30 percent of patients with acute leukemia[2,6] manifest involvement of the nervous system, we have noted symptomatic neurological involvement in nearly 50 percent of these patients.

From the Department of Medicine, University of California, Irvine, California College of Medicine, Irvine, and the Department of Medicine, Case Western Reserve University, Cleveland.

Submitted revised January 7, 1974.

Reprint requests to: S. A. Armentrout, MD, Department of Medicine, University of California, Irvine, 101 City Drive South, Orange, CA 92668.

Methods and Therapy

During 12 months, 17 consecutive patients with acute granulocytic leukemia were observed by the authors. The diagnosis was made or verified by bone marrow and peripheral blood studies by one of the authors. Neurological complications were verified by staff neurologists and appropriate investigations of the nervous system were carried out. All patients were treated with cytosine arabinoside administered intravenously or intrathecally.

Intravenously administered cytosine arabinoside was given in a dose of 4 mg per kgm, infused over an eight hour period daily. The total length

of each course of therapy was determined by peripheral blood and bone marrow response. Several patients were given repeated courses of this drug. Intrathecally administered cytosine arabinoside (100 mg into the lumbar subarachnoid space) was used when pleocytosis of the cerebrospinal fluid, with or without neurological signs, was present. Repeat intrathecal injections were given if needed. Some patients also received localized radiotherapy to the central nervous system. A dosage of 500 rads to the cranium and 1500 rads to the spinal column was administered where necessary.

In four cases in which autopsy studies were done, there had been clinical neurological manifestations. Leukemia patients without neurological symptoms and signs did not have extensive studies of the central nervous system (such as lumbar puncture, brain scan and arteriogram) beyond the usual clinical neurological examination.

Definitions

Remission implies an absence of immature granulocytic cells in the blood. A bone marrow remission implies the elimination of leukemic cells from the bone marrow with a reduction of immature blast forms to normal limits.

Some investigators equate "meningeal leukemia" with increased cerebrospinal fluid cellularity. However, we reserve the term for those conditions, as described by Shaw[7] in which there are symptoms or signs of neurological disorder, especially those with increased intracranial pressure associated with increased cells not explainable by infections. "Granulocytic meningeal leukemia" is usually associated with the presence of immature granulocytes in the cerebrospinal fluid.

Reports of Cases

Two case histories are presented to illustrate the neurological problems that might arise during the course of acute granulocytic leukemia.

Case 1. A 20-year-old woman was treated in June 1969 with 6-mercaptopurine, for acute granulocytic leukemia. Following a brief incomplete remission, she was treated with cytosine arabinoside to complete hematologic remission. Headache, nausea and vomiting developed in November 1969 and continued through March 1970 when she was readmitted to hospital with a hematologic relapse. Lumbar puncture showed normal pressure, spinal fluid protein content of 90 mg per 100 ml, cerebrospinal fluid (CSF) sugar of 25 mg per 100 ml and 250 cells which were morphologically leukemic "blast" cells. Cultures were negative. Cytosine arabinoside given intravenously induced a complete hematologic remission, and intrathecally administered cytosine arabinoside induced a return to normal in the cerebrospinal fluid and a moderate reduction in symptoms within one week.

After two and a half months, cyclophosphamide (Cytoxan®) was administered intravenously because of diplopia (right VI nerve paresis), blurred vision, headache and right exophthalmos. There was prompt relief of symptoms. Two months later, in August 1970, the patient was admitted to hospital with severe headache, confusion, stiff neck, incontinence and perseveration. There were no focal neurological signs, but lumbar puncture showed spinal fluid protein content of 115 mg per 100 ml, occasional leukemic blast cells and pressure elevated to 350 mm of water. A right retrobrachial arteriogram showed "mild" lateral ventricular dilatation. Corticosteroid therapy was begun, with improvement within 18 hours. A radioiodinated serum albumin study (RISA scan) was done, but no isotope could be detected intracranially after 24 hours. During the next 36 hours the patient became progressively more confused, had blurred vision and suddenly became totally blind, with fixed dilated pupils. Intravenously administered urea followed by ventricular shunt resulted in complete neurological remission except for blindness. Radiation therapy was administered to the entire head. The patient has remained in hematological remission without further progression of neurologic disease.

Case 2. Nine months before admission to hospital, the patient, a 42-year-old man, was discovered to have acute granulocytic leukemia. Two hematologic remissions were induced with 6-mercaptopurine, corticosteroids and vincristine. On admission the patient was in hematologic relapse with neurological signs and symptoms including singultus, diplopia (right VI nerve paresis), numbness of the tongue, headache, right facial and palatal weakness, and diminished pain sensation of the left lower face. Lumbar puncture showed only a slightly elevated spinal fluid protein content. A retrobrachial arteriogram and RISA scan were within normal limits. Hematologic remission was induced with intravenously administered cytosine arabinoside, but giving cytosine arabinoside intrathecally did not improve the neurological symptoms or signs. Radiation ther-

TABLE 1.—*Duration of Leukemic Process Before Development of Neurological Symptoms and Duration of Leukemia from Time of Diagnosis*

Case	Age, Sex	Neurological Symptoms	Duration of Leukemia* before Neurological Signs (Months)	Months to Death	Months Alive
1.	20♀	+	4	–	19
2.	42♂	+	8	9	..
3.	20♀	+	0 (at onset)	21	..
4.	55♀	+	5	7	..
5.	20♀	+	2	15	..
6.	66♂	+	0 (at onset)	6	..
7.	80♂	+	2	3	..
8.	60♂	+	1	6	..
9.	27♀	–	–	–	3
10.	48♀	–	–	6	..
11.	18♂	–	–	–	3
12.	74♂	–	–	9	..
13.	48♀	–	–	6	..
14.	42♀	–	–	–	4
15.	53♀	–	–	2	..
16.	66♂	–	–	2	..
17.	63♂	–	–	3	..

Neurological Signs and Symptoms: + Present – Absent
*Duration from the initial diagnosis to the development of neurological signs.

TABLE 2.—*Neurological Symptoms and Signs in Eight Patients*

Symptoms:	
Headache	7
Abnormal Mental Status	4
Weakness	3
Sensory Abnormality	2
Visual	1
Signs:	
Cranial Nerve Paresis	6
Paraparesis	4
Nuchal Rigidity	2
Sensory Neuropathy	2
Incisural Herniation	2
Brain Stem Signs	1
Motor Neuropathy	1

TABLE 3.—*Response to Therapy*

Case	Therapy	Response (Cerebrospinal fluid)	Response (Signs and Symptoms)
1.	Intrathecal (Cytosine Arabinoside) Radiation	+	+
2.	Intrathecal (Methotrexate)	+	±
	Intrathecal (Cytosine Arabinoside)	+	–
	Radiation	+	+
3.	Intrathecal (Methotrexate)	±	±
	Intrathecal (Cytosine Arabinoside)	+	–
4.	Intrathecal (Cytosine Arabinoside)	+	–
5.	Intravenous (Cytosine Arabinoside)	*	+
6.	Intrathecal (Cytosine Arabinoside)	+	±
	Radiation	+	+
7.	Not Treated	*	–
8.	Intrathecal (Cytosine Arabinoside)	+	–

+ Reponse – None ± Equivocal * Not Observed

apy, however, caused complete regression of these findings. Two months later the patient died in relapse from the disease. Postmortem examination failed to find any gross or microscopic abnormality of the nervous system.

Results

Table 1 shows the duration of the leukemic process before the development of neurological symptoms and the duration of leukemia from the time of diagnosis for the patients of this series. Eight of the 17 patients had evidence of neurological involvement (47 percent of the group). The average time from diagnosis to death in the group with neurological symptoms was 9.8 months, and in those without neurological symptoms it was 3.6 months. This would suggest that the neurological symptoms may be related to a longer life span, an association also noted by Evans.[8]

Clinically, the types of neurological disorders observed were paraparesis, increased intracranial pressure (with and without herniation), extraocular paresis and paralysis, bladder and bowel incontinence, headache, facial paralysis, palatal paralysis, signs of meningeal irritation, sensory (including hypersthesias, hypalgesias, and pain) and motor neuropathy. The frequency of these is shown in Table 2.

The relationship of the neurological signs and symptoms to treatment with antimetabolites, radiation or both is shown in Table 3. It is of interest that, with the exception of two patients, the intrathecal or intravenous administration of cytosine arabinoside bore no direct relationship to the relief of neurological symptoms. Radiation therapy to localized areas or to the entire cerebrospinal axis did relieve symptoms partially or completely in all instances. We found no benefit from prophylactic intrathecal antimetabolite therapy in preventing the development of neurological disability. This agrees with findings for lymphocytic leukemia in childhood reported by Milhorn and Gross.[9]

Discussion

Neurological involvement in acute granulocytic leukemia is well known and occurs with greatest

frequency in the central nervous system. Central nervous system hemorrhage and infection are reported to cause 80 percent[10] of all deaths in patients with leukemia. The intracerebral hemorrhages that are often related to intravascular leukostases and leukemic nodules, and associated with leukocyte counts more than 100,000 per cu mm in peripheral blood[10,11] were not seen in any of these autopsy studies. In addition, there was no suggestion from clinical or autopsy studies of subarachnoid, subdural or epidural hemorrhage. These are frequently associated with a very low platelet count,[10] often in the presence of peripheral leukocyte counts below 50,000. The absence of these complications may be related to two factors: first, the early institution of antimetabolite therapy with cytosine arabinoside when the leukocyte count in peripheral blood became significantly elevated and, second, the use of platelet transfusions when symptomatic thrombocytopenia occurred. Only one autopsy study showed extensive central nervous system involvement. This consisted of leukemic infiltration of the meninges and acute hydrocephalus.

Wells and Silver[12] state that 25 to 50 percent of all patients with leukemia have neurological manifestations, and though this incidence is higher than that reported by most other investigators, it is of interest in this regard that the frequency of central nervous system problems reported in patients with acute leukemia, especially in children, has increased significantly during the past few years.[13]

Meningeal leukemia (Cases 1 and 4, Table 1) appears with more frequency in patients with acute lymphocytic leukemia than in those with acute granulocytic leukemia.[14]

The cerebrospinal fluid findings in leukemic patients must be carefully evaluated since bacterial meningitis, abscess formation or fungal disease occur with increased frequency. Cerebrospinal fluid pleocytosis, chemical abnormalities (elevated protein and low sugar) and elevated pressure may be present in these potential complications of the disease or its therapy. Appropriate cultures and stains, and the response to radiation and chemotherapy, are often helpful in diagnosis. Abscesses can often be detected by brain scans, electroencephalograms and arteriography. In most patients with meningeal leukemia, the authors were able to identify cerebrospinal fluid cellular morphology by high power microscopic examination while performing a cell count in the hemocytometer. Occasionally the use of a simple stain, such as Wright's stain, may help to define the cellular morphology of the immature granulocytes more easily. The identification of these immature granulocytes, morphologically identical to the granulocytic "blast" cell or leukemic leukocyte found in bone marrow or peripheral blood, makes it unlikely that an infectious process is present. These immature cells do not participate in the response to an infectious process. A simple method to examine cells found in cerebrospinal fluid that are not readily identified by routine methods may be of help and should be used when unidentifiable atypical cells are noted after lumbar puncture.[7]

Results of radioiodinated serum albumin studies (RISA scans) done in two patients with symptoms of increased intracranial pressure were inconclusive. One of these patients was subsequently shown to have increased intracranial pressure at surgery (Case 1). Obstruction at the foramen magnum may have contributed to the failure of this procedure. In the same patient with acute hydrocephalus, a retrobrachial arteriogram failed to show ventricular dilation. Although it is possible that adequate time had not passed to allow for ventricular enlargement, the symptoms of nausea, vomiting and headache had been present for at least two months.

These cases suggest that abnormal neurological manifestations and cerebrospinal fluid findings (pleocytosis and elevated pressure) should alert the physician to impending cerebral herniation or other complications of increased intracerebral pressure. In the presence of these two findings, the possibility of a surgical shunting procedure should be considered at the first signs of herniation or focal findings. Hydrocephalus is not uncommon when the meninges have been involved by an infectious process, and similar arachnoidal obstruction by leukemic cells may explain the phenomenon in the present cases.

In this group of patients, it appears that intravenous and intrathecal cytosine arabinoside therapy alone was inadequate to relieve neurological symptoms. Subjective improvement after intrathecal administration of cytosine arabinoside occurred in only two of these patients. This finding may be extremely important in the proper management of meningeal leukemia in adults. In three of our leukemic patients, abnormalities of extraocular movement were noted but only one of these patients had any remission of symptoms

after antimetabolites were given intrathecally. Radiation therapy, on the other hand, caused both subjective and objective improvement in all cases.

As stated, the incidence in this series of neurological symptoms and signs associated with acute granulocytic leukemia was nearly 50 percent. This may be related to one or more possible factors. Since some patients with this disease have had a significant increase in life expectancy, the chance for the development of neurological involvement is perhaps greater. The increased incidence of neurological disease might also be related to the greater attention given to symptoms of neurologic disease in these cases of leukemia. A third possibility is that the antimetabolites used in the therapy of this disease could induce neurological complications. The mechanism of the neurological damage in leukemia is debated. Some investigators feel that ischemia secondary to blood vessel occlusion is responsible.[6,10,15] Direct involvement of the nerves by leukemic cells in the regions where symptoms have occurred is not frequently seen in postmortem examinations.[10] This was true in the present study in three out of four autopsy studies.

Physicians should be acutely aware of central nervous system symptoms in patients with acute granulocytic leukemia. This is especially important for those patients in whom adequate peripheral remissions have been induced with chemotherapeutic agents, since these complications may be treatable by medical or surgical procedures, with a decrease in both morbidity and mortality.

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Refer to: Panish JF, Berci G: Non-invasive colonoscopic polypectomy—Review of 100 cases. West J Med 121:6-9, Jul 1974

Non-Invasive Colonoscopic Polypectomy

Review of 100 Cases

JOEL F. PANISH, MD, *and* GEORGE BERCI, MD, *Los Angeles*

Colonoscopic polypectomy was done in one hundred patients. One hundred eighty-three polyps were removed from these patients during 111 colonoscopies and eight malignant polyps were found. The material suggests that pedunculated malignant polyps, when the stalk is clear of carcinoma, can be cured through colonoscopic polypectomy, thus obviating the need for laparotomy. At present, however, more cases and a longer follow-up are needed before this can be established. There were no deaths and no perforations. There were two cases of bleeding, only one requiring transfusion.

The procedure costs less and entails less time in hospital than laparotomy, colotomy and polypectomy.

THE DIAGNOSTIC capability of fiber-optic colonoscopy is now well established.[1,2] In addition, its therapeutic use in the removal of colonic polyps by a cautery snare introduced through the colonoscope has been reviewed and appears to be safe and practical.[3]

Material and Methods

The series here reported comprises the first 100 consecutive patients encountered in the first year of our experience with this procedure. It represents a total of 111 colonoscopies for removal of 183 colonic polyps. The Olympus CF-LB (187 cm fiber-optic colonoscope), the ACMI light source FO-1000 and the Storz cautery snare with the EMS electro-surgical unit were used in 82 cases. The Olympus CF-LB colonoscope with CL-3 light source and the Cameron-Miller electro-surgical unit were used in 29 procedures.

The indications for colonoscopy and polypectomy were the appearance on barium enema examination of one or more polypoid lesions in the colon measuring more than 1 cm in diameter, or any polypoid lesion regardless of size if there was a previous history of colonic polyps, colonic carcinoma or a family history of colon polyps or carcinoma.

Preparation of patients consisted of a clear liquid diet for three days, a laxative at 4 pm the day before the polypectomy and cleansing tap water enemas three hours before the procedure. In only two cases was the tract insufficiently clean after this routine, and in those cases the procedure was postponed until further colonic cleansing was carried out. The usual routine has been to admit patients to hospital the afternoon before the procedure and discharge them 24 hours after it.

From the Department of Gastroenterology (Dr. Panish), and the Department of Surgical Endoscopy (Dr. Berci), Cedars-Sinai Medical Center, Los Angeles.

Submitted February 4, 1974.

Reprint requests to: G. Berci, MD, Director, Department of Surgical Endoscopy, Cedars of Lebanon Hospital, 4833 Fountain Avenue, Los Angeles, CA 90029.

In four patients with long pedunculated sigmoid polyps the polypectomies were done on an outpatient basis. Normal diet was resumed immediately after the procedure in those cases where there was no indication of bleeding or perforation. Patients were allowed to resume sedentary work 48 hours after polypectomy and all physical activity within five days.

The procedure was not done in patients with acute diverticulitis or colitis. We have found that in certain patients it may be difficult, or impossible, to advance the colonoscope beyond the distal sigmoid, because of pelvic colon immobility secondary to previous pelvic surgical operations or treatment with radiation. However, this can only be ascertained at the time of colonoscopy itself, not from barium enema examination alone.

Most patients were given meperidine (Demerol®) and diazepam (Valium®) intravenously just before the procedure. The dosage was titrated to produce a relaxed state, but no somnolence. The patients' tolerance and acceptance of the procedure were excellent.

The actual time spent doing the procedure varied from 20 minutes to four hours and was related to the anatomical configuration of the colon, the number and position of polyps and degree of the examiner's experience. The average time was approximately half an hour.

Fluoroscopy was invaluable in certain cases and only those patients with polyps in the sigmoid colon had polypectomies done without fluoroscopy readily available.

It is not the purpose of this paper to review in detail the various techniques that have already been published.[1,2,3]

Results

There were 68 men and 32 women in the series. The ages of the men ranged from 44 to 88 years (average: 66.9 years) and the ages of the women ranged from 36 to 83 years (average: 59.2 years).

The 100 patients had 111 colonoscopies, 92 patients having one colonoscopy each, five patients having two each and three having three each. A total of 183 polyps were removed. Eighty one percent of the polyps were recovered from the entire series, but this proportion increased from 76 percent in the first 50 patients to 94 percent in the second 50 patients.

In the first half of the study, we did not recognize that many polyps we thought were being lost in the colon lumen were actually being suctioned back through the suction channel of the colonoscope into the suction bottle in a fragmented form. When we began to look for these polyps at the end of the procedure, and filtered the contents of the suction bottle, our recovery rate improved significantly (Table 1). It is important to note that of the 35 polyps not recovered, all were less than 1 cm in size and two thirds of these (22) were under 0.5 cm. Almost all were discovered incidentally at colonoscopy, and were not seen on barium enema examination. These incidental polyps were not the reason for colonoscopy.

The vast majority of polyps were found in and removed from the sigmoid area, with the number decreasing as the distance from that site increased (Table 2).

Histologic classification of the removed polyps showed that the majority were benign adenomas (Table 3). In six polypoid lesions it was found that part of the benign adenoma showed carcinomatous changes. These polypoid lesions, therefore, were partially benign and partially malignant. Similar changes indicating the presence of both villous adenoma and carcinoma were found in two polyps. Two of the three lipomas had definite stalks. These polypoid lesions are usually distinguishable because the "head" of the polyp

TABLE 1.—*Results of Colonoscopic Polypectomy*

	No. of Polyps	*Percent*
Polyps removed	183	100
Polyps recovered	148	81
First 50 patients	84	76
Second 50 patients	64	94
Polyps lost	35	19
Under 0.5 cm	22	
Under 1.0 cm	13	

TABLE 2.—*Polyp Location*

	No. of Polyps
Sigmoid colon	105
Descending colon	33
Transverse colon	30
Ascending colon	8
Cecum	7

TABLE 3.—*Histologic Classification of Removed Polyps*

	No. of Polyps	*Patients*
Adenoma	129	67
Villous adenoma	5	5
Atypical adenoma	1	1
Carcinoma in adenoma	6	6
Carcinoma in villous adenoma	2	2
Lipoma	3	3
Inflammatory	2	2

is much softer and more pliable than that of the ordinary adenoma. Almost half of the polyps were between 1 and 2 cm in size (Table 4). The distribution of the number of polyps per patient is shown in Table 5. Thirty percent more polyps were found during colonoscopy than had been shown by barium enema examination.

Bleeding occurred in two patients. In one, the bleeding was arterial and immediately apparent at the site of polypectomy. This patient required two units of blood. We believe that vasopressin (Pitressin®), administered intravenously, was helpful in arresting this arterial bleeder. The second showed a blood loss of 200 ml through the rectum 72 hours after the polypectomy. The patient was observed and required no treatment. No perforations occurred in this series.

An analysis of the malignant polyps found is given in Table 6. Eight polyps in eight different patients showed malignant changes, an incidence of 8 percent in relation to the number of patients and 5.7 percent in relation to the number of polyps recovered. Two of these were located in the sigmoid colon, four in the descending colon and two in the transverse colon. No malignant changes were found in polyps under 1.2 cm in size. The number of polyps in the patient did not seem to have any relationship to the occurrence of carcinoma. Fifty percent of the lesions were sessile, 50 percent pedunculated. Seven of the malignant conditions were the type in which carcinoma occurred in an adenoma. One was a carcinoma in a villous adenoma.

Six of the eight patients have had resection. In four of these cases no residual malignant lesion was found in the pathologic specimen, even though the stalk showed invasion; malignant tissue seemed to have been cleared at the time of cautery snare removal through the colonoscope. In one patient a residual tumor was found during surgical operation, but results from tests of adjacent lymph nodes were negative.

In one patient with carcinoma occurring in a villous adenoma, one microscopic focus of carcinoma was found in the submucosa. However, the lymph nodes were free of disease. Two patients have refused operations. One of these patients was examined with a colonoscope six months after removal of a polyp through the colonoscope. Malignancy had originally invaded the stalk but it was felt to have cleared. No lesion was observed on repeated examinations. The other patient who refused operation was examined by colonoscope three months after partial polypectomy and ful-

TABLE 4.—*Polyp Size*

Centimeters	*No. of Polyps*	*Percent*
0.5	11	6.0
0.5-0.9	40	21.8
1.0-1.9	87	47.5
2.0-2.9	27	14.7
3.0-3.9	9	4.9
4.0-4.9	4	2.3
5.0	5	2.8

TABLE 5.—*Number of Polyps per Patient*

No. of Polyps	*Patients*
1	66
2	18
3	9
4	3
5	1
6	1
10	2

TABLE 6.—*Analysis of Malignant Polyps*

Date	*Size*	*Location*	*Polyps in Patient*	*Gross*	*Microscopic*	*Follow-up*
4/72	1.5 cm	Descending colon	1	Stalk	Carcinoma in adenoma superficial	Surgical operation no lesion
6/72	4.0 cm	Sigmoid colon	10	Sessile	Carcinoma in adenoma not cleared	Surgical operation tumor left, no nodes
9/72	1.2 cm	Sigmoid colon 2	1	Stalk	Carcinoma in adenoma stalk invaded, but cleared	Surgical operation no lesion
9/72	1.3 cm	Descending colon 4	1	Stalk	Carcinoma in adenoma stalk clear	Surgical operation no lesion
3/73	1.5 cm	Descending colon	1	Stalk	Carcinoma in adenoma stalk invaded, but cleared	Re-colonoscoped 6 months—no lesion
8/73	5.0 cm	Transverse colon	2	Sessile	Carcinoma in adenoma stalk invaded, ? cleared	Surgical operation no lesion
8/73	1.5 cm	Descending colon	1	Sessile	Carcinoma in adenoma ? cleared	Re-colonoscoped after 3 months—recurrent lesion

guration. The lesion had reoccurred and was coagulated again. This patient continues to refuse operation, and further follow-up is planned.

Discussion

We have found colonoscopic polypectomy to be a safe and efficient procedure. It is well tolerated, even by elderly, high-risk patients. The procedure at times is difficult and time-consuming. We would advise, therefore, that only those who have had gastrointestinal endoscopy experience should undertake it.

Our findings are similar to those reported by other investigators as to size, location, pathologic features, complications and incidence of malignancy in colonic polyps.[3]

It is too early to ascertain whether complete removal of malignant adenomatous polyps by colonoscopic cautery snare will prove to be a curative procedure. At present we would advise that patients with malignant changes be treated by laparotomy and segmental resection. Long-term follow-up of a significant number of cases is needed to show whether we are removing these lesions completely enough and, therefore, whether localized carcinoma in pedunculated adenomatous polyps can be cured without operation.

Colonoscopic polypectomy, as a non-invasive procedure, has major advantages over laparotomy, colotomy and polypectomy. The average length of time spent in hospital in our series was 36 hours and the average time lost from work was 48 hours. The patient usually is able to return to regular activity in 72 hours. A normal diet is resumed on the first day after polypectomy and the cost to the patient or the insurance carrier is reduced by approximately 75 percent.

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Acute Renal Failure

If the patient in acute renal failure starts to get in trouble, don't hold off dialysis too long, because if you do, you can lose the patient in a hurry. Most facilities have hemodialysis, or you have access to it in your area. It's lifesaving in certain instances. In all instances, it simplifies the care and minimizes most of the problems. Just a last word about perhaps stopping these lesions in things we do all the time. Here I specifically refer to the infusion urogram and the renal angiogram in the individual who already has renal insufficiency . . . and the main problem here is that the studies are done when the individual is dehydrated. So the main thing is to avoid sending the patient to the X-ray department in a dehydrated state. On the angiogram, you might ask the radiologist if, in this patient, he might not do his injection a little bit higher in the aorta rather than right at the level of the renal arteries . . . or perhaps just barely above.

—Lynn H. W. Banowsky, md, *Cleveland*
Extracted from *Audio-Digest Surgery*, Vol. 21, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Rom WN, Palmer PES: The spectrum of asbestos-related diseases. West J Med 121:10-21, Jul 1974

The Spectrum of Asbestos-Related Diseases

WILLIAM N. ROM, MD, MPH, *Sacramento*
and
PHILIP E. S. PALMER, FRCP (Edin), FFR, *Davis, California*

Diseases caused by exposure to asbestos are prime examples of environmentally-related illnesses. Asbestos produces asbestosis from large exposures over short latent periods; it acts as a carcinogen from small exposures over long latent periods; and it induces mesothelioma with minute exposures. Its presence as the magic mineral is ubiquitous in our modern society.

Asbestos, An Environmental Contaminant

Man has used asbestos for centuries. The wicks of the oil lamps of the vestal virgins were asbestos. It was used in Finland as a pottery cement 4,500 years ago. It was used in 28 B.C. by a Greek doctor for acoustic insulation. It is almost inevitable that that remarkable traveler Marco Polo came upon asbestos mines in Siberia. It is equally unsurprising that it was regarded as a curiosity and the subject of witchcraft until the end of the 17th Century.[1] Its commercial use began when serpentine asbestos was discovered in Canada and used in the conservation of heat. Its use can thus be traced throughout all history, but in the last 100 years it has increased a thousand times, and in the last 15 years its use has probably increased geometrically.[2]

Asbestos has been aptly called "the lethal dust"[1] because of its ability to cause crippling respiratory disease and because of its association with malignant disease of the lungs, the pleura, the peritoneum and the alimentary tract. Editorials on its dangers abound and grim warnings of its hazards are found in the medical journal of every specialty in every language throughout the world. And yet man continues to use it, and many doctors are only dimly aware of its potential for causing disease.

Asbestos is everywhere.[3] This fact was first sharply focused by a series of consecutive autopsy studies carried out first in Cape Town, South Africa, and then in Miami, Florida. It was shown that asbestos could be found in the lungs of 30 percent of all men and 20 percent of all women

From the Department of Internal Medicine, Sacramento Medical Center and University of California, Davis, School of Medicine (Dr. Rom); and the Department of Diagnostic Radiology, University of California, Davis, School of Medicine (Dr. Palmer).

Submitted, revised, March 8, 1974.

Reprint requests to: W. N. Rom, MD, MPH, Sacramento Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817.

who died in these cities.[4] Subsequently, asbestos was found in 41 percent of an autopsy series in Pittsburgh. Similar statistics resulted from autopsy series in New York, Montreal, Belfast and London.[5-9] Asbestos should be considered almost a normal postmortem finding in the lungs of urban dwellers. It has become such a "normal" finding that one wonders why the citizens of Perugia in Italy manage to escape? For there, only 1 percent of the population harbors asbestos when they die.[10]

There are 400 factories making asbestos in America. They employ 31,000 people directly in the manufacture of more than 3,000 different articles. But these are not the only workers at risk. Another five million, mainly in the construction industry,[11-13] are exposed in their work to significant levels of asbestos.

Moreover, asbestos fibers have been found in beer, sherry, soft drinks and tap water.[14] Fibrils were found in six out of seventeen samples tested of commercially available parenteral medications, presumably a result of asbestos filtration.[15] Asbestos is found in the antifreeze used in our cars, is a hazard for dental nurses, is used in plastics and for manufacturing brake linings. It has been used in the construction of homes and commercial buildings, as well as in ships, in every type of insulation and refrigeration, and for the production of papers and textiles.[13,16] It is contained in sewer pipes, used in surfacing roads and is found in many types of paint sprays. Furthermore, it is not necessary to work in contact with this material to be at risk, for someone in your household may bring it into your atmosphere. Merely washing clothes that are heavily contaminated with asbestos may bring the danger of malignant disease.[17]

We are surrounded by asbestos in the course of our normal lives. Not only do we inhale it or rub talc containing asbestos onto our skin, but occasionally we even swallow it. In Japan, for instance, rice is often treated with a substance containing tremolite and anthophyllite asbestos to enhance the flavor. It has been suggested that there may be a link between this custom and the high rate of cancer of the stomach in Japan.[18] Of course, there are so many factors involved in this condition that such a relationship must remain pure speculation.

Animals have not escaped: one would expect to find asbestos in donkeys or mules that work in an asbestos mine, but it has also been found in baboons and rats living in the hills surrounding the mills in the northwest part of the Cape Province of South Africa.[19] (A full description of the contamination of the atmosphere by asbestos has been provided by Paul Brodeur in *Asbestos and Enzymes*.[20,21])

Characteristics of the Mineral

Asbestos is a commercial term covering some 30 silicate compounds occurring in serpentine and amphibole rocks. Only six have economic significance. One of these, chrysotile, is fibrous and when examined through an electron microscope is seen to have hollow fibers rolled in sheets of varying length.[22] Chemically, chrysotile is hydrated magnesium silicate containing some iron oxide, magnesium and aluminum. The other five commercially significant asbestos compounds all come from amphibole rocks. Crocidolite, one of the five, differs from chrysotile because it has solid fibers arranged in bundles, which are more than twice the diameter of the fine, hollow chrysotile fibers.[22] These five other products differ mainly in the quantity of calcium or iron which each may or may not contain.[23]

Commercial asbestos is almost always mixed, and chrysotile provides 95 percent of industrial asbestos. It is a very flexible product with high tensile strength and heat resistance. It is resistant to moisture, to the corrosive action of acids, and is of course incombustible.[24]

It seems probable that the characteristics of the fibers as well as the chemical nature of compounds may have significance in causing disease. The particle size is also important, but perhaps the ratio of volume to mass (some fibers are hollow whereas others are solid) is more important. This ratio may vary as much as a factor of three. This will affect not only the airborne concentration, but the behavior of dust in the air, the pattern of its inhalation, and quite possibly its subsequent behavior in the body. This significance may be dramatically shown by noting that one pound of asbestos from the northern part of the Cape Province in South Africa may contain as much as 30 times the number of fibers as the same weight of asbestos from the geographically nearby Transvaal.[25] There is a great geographical difference in the pattern of disease resulting from asbestos inhalation and one may postulate that this results from physical and chemical variations, as well as from other factors such as smoking and intercurrent disease.[26] To enable research to progress, the International League Against Cancer (UICC) has

Figure 1.—Asbestos or ferruginous body in cytologic examination of sputum of asbestos worker. (Oil immersion, reduced 50 percent from ×1500)

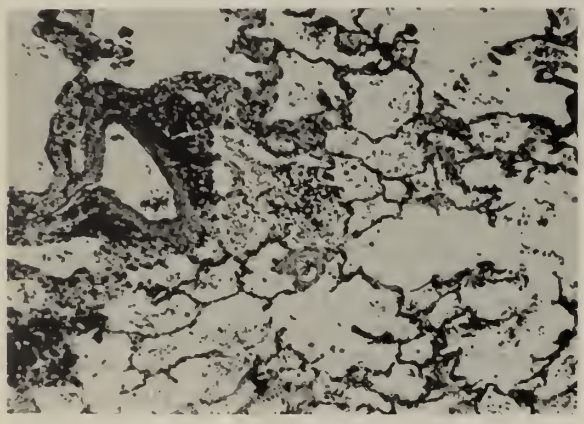

Figure 2.—Lung from autopsy specimen showing thickening and edema of the interlobular and alveolar septa, occasional asbestos bodies and many alveolar spaces filled with macrophages. (Hematoxylin and eosin, reduced 50 percent from ×400)

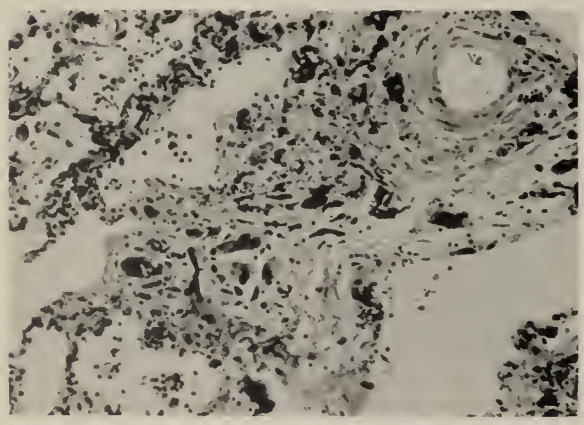

Figure 3.—Lung from autopsy specimen showing clubbed asbestos bodies, dense fibrosis and extensive collagenisation. (Hematoxylin and eosin, reduced 50 percent from ×700)

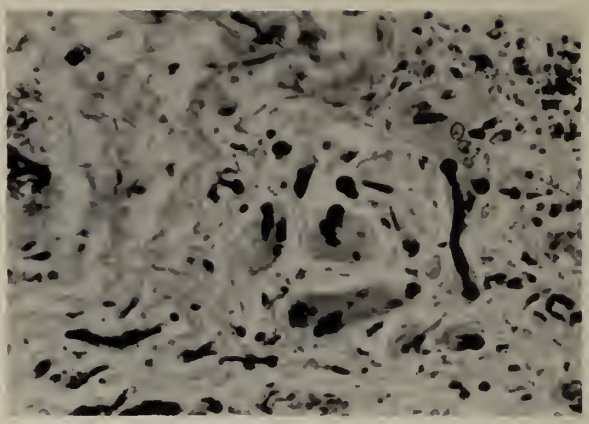

Figure 4.—High power view of asbestos bodies with alveolar wall thickening and numerous macrophages laden with a coarse granular material in the alveolar spaces. (Hematoxylin and eosin, oil immersion reduced 50 percent from ×1500)

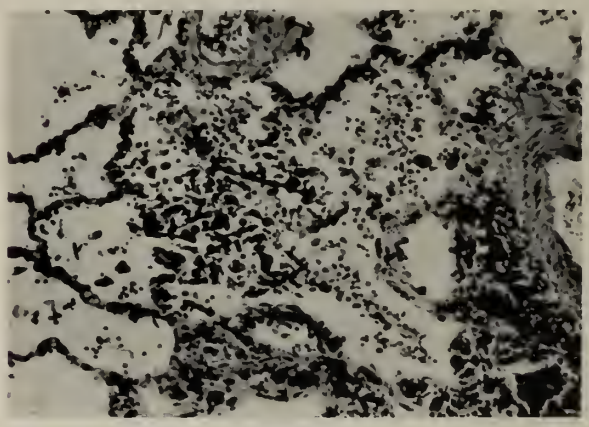

Figure 5.—Asbestos bodies shown in advanced fibrosis with collagenisation apparent. (Reduced 50 percent from ×700)

provided standard samples of various types of asbestos for research.

Closely associated with the chemical combination and the particle size, is the ability of the asbestos fibers in the virgin state to adsorb hydrocarbons subsequent to mining, as well as the varying contents of oil, waxes and other organic matter contained within the fibers themselves. Chrysotile can absorb the carcinogen 2-4 benzpyrene, and such compounds are found adsorbed to native crocidolite and amosite.[27,28]

One theory to account for the difference in carcinogenic risk between asbestos found in South Africa and that in Canada was based on the idea that jute bags used for shipping South African asbestos contain carcinogenic oils which later become adsorbed, whereas the fibers from Canada

are shipped in plastic bags.[27] This theory is untenable, because the fibers are equally carcinogenic in South Africa before they have been put into the jute bags and shipped.

Tissue Reaction

The initial tissue reaction to asbestos fibers is a fluid exudation with an inflammatory response that coats the particle with a protein film. In guinea pigs, under experimental conditions, this process takes about seven days but it may take longer in human beings. The protein film is impregnated with iron and becomes a golden brown "asbestos" or "ferruginous" body.[29] If the fibers are of a suitable size, they are then phagocytized by alveolar macrophages. Fourteen days after the guinea pig inhalation of the fibers there is a progressive bronchiolitis which proceeds to collagenisation and fibrosis. Later the paratracheal nodes become involved, and electron microscopy has shown that the microscopic fibers travel through the lymphatics to these regional nodes. They may cause more tissue injury than the larger and more obvious fibers which are found in the lung and sputum. Fibrosis occurs initially in the lung bases and then progresses upwards as the disease spreads. One of the difficulties in the diagnosis of asbestosis is that the "ferruginous body" can be caused by fibers other than asbestos.[30] Such bodies are found in the lungs of coal miners and those who work with graphite, fiberglass, ceramics, carborundum and even diatomaceous earth.[30] Thus, it is not safe to diagnose asbestosis merely by the presence of "ferruginous bodies" in the sputum or lungs, particularly as asbestosis is almost a normal finding in city dwellers (Figures 1-5).

Pulmonary Asbestosis

The first case of pulmonary asbestosis reported was from the Charing Cross Hospital in London in 1900.[1] The name was first given to it by Dr. W. E. Cooke in 1924, referring to a woman who had died after twenty years of working as an asbestos textile operator.[31] Fifty years later it is still a very difficult disease to define. Many authors adopt their own criteria, adding to the confusion in the literature. Murphy[32,33] devised a definition which has much to recommend it. He required at least three of five criteria:

1. Dyspnea after climbing one flight of stairs.
2. Fingernail clubbing with a hyponychial angle greater than 198°.
3. Rales present in two or more of eight sites.
4. A forced vital capacity less than 80 percent of the predicted level.
5. A radiographic film of the chest showing moderate or advanced asbestosis.

To overcome the radiological problem of defining asbestosis, he required that three radiologists assess the film separately and assign a score of five or six on a six point arbitrary scale.

Pulmonary function studies are helpful in making the diagnosis. The most consistent finding is a decrease in the diffusing capacity for carbon monoxide. This correlates highly with the level of dyspnea.[34] The total lung volume is reduced, probably by the fibrotic reaction both in the lungs and in the pleura causing reduced thoracic expansion. There is also a considerable ventilation-perfusion inequality, and the alveolar-arteriolar difference is characteristically increased.[34] A very consistent finding is reduction in the forced vital capacity (fvc) and the forced expiratory volume in one second (fev-l).[36] It is known that asbestosis causes a pronounced reduction in pulmonary compliance, presumably from the reduction in the total number of lung units and their mechanical restriction by interstitial and pleural fibrosis.

Field surveys to identify workers who have been affected by asbestosis have been successful using a simple spirometer to determine the fvc and the fev-l, providing a ratio of fev-l to fvc as a percentage. For example, in a study of 57 wall board manufacturers, Wegman et al found that the duration of exposure to asbestos was more reliably related to the loss of fvc and fev-l than age, height or smoking. They found that the mean of fev-l to fvc was 76.3 percent and that only three of the 57 workers had figures below 60 percent (60 percent or below is taken as being characteristic of obstructive disease[36]).

The symptom complex is manifested mainly by dyspnea, although this is usually a late occurrence. In a series of 1,170 asbestos workers, some of whom smoked and some of whom did not, dyspnea developed in 1 percent after ten years of exposure, in 7 percent after 20 years and in over 50 percent of those who survived after 40 years.[37] Finger clubbing, cyanosis and fine basal rales all occur somewhat late.[38] An obvious bronchitis is relatively infrequent in contrast to other types of pneumoconiosis. An asymptomatic and non-inflammatory bronchiectasis can occur as a result of distention of the bronchi and bronchioles caused by the contraction of the interstitial fibrous tissue. It is a little surprising that obstructive pulmonary

Figure 6.—A pneumothorax leaving visible pleural calcification on the parietal pleura.

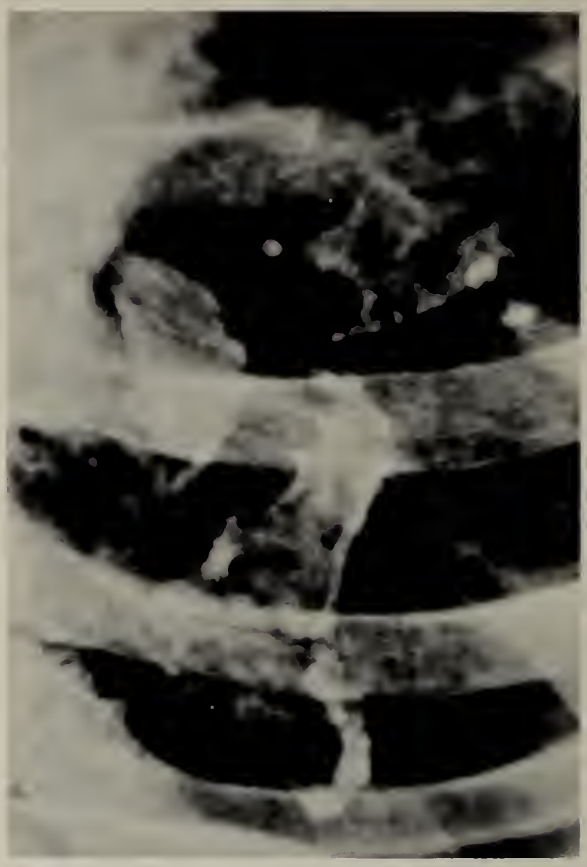

Figure 7.—The typical "leaf" pattern of asbestos pleural calcification with a rolled edge.

emphysema is not a feature of asbestosis, although the alveolae do become distended and distorted by the fibrosis in the same way as the bronchial tree. This fibrosis is truly interstitial, and the differential diagnosis histologically must include any of the many other causes of similar fibrosis.

Asbestos pleural effusion has been noted in 21 percent of all patients with asbestosis in one laboratory. It is frequently recurrent, usually bilateral, accompanied with chest pain and composed of a sterile exudate.[39]

Radiographic Signs in Pulmonary Asbestosis

There is yet no international definition of the radiographic changes of asbestosis. Many radiological features have been described, but since there is no basis on which to define "asbestosis" these findings cannot be satisfactorily correlated. If 50 percent of the urban population have asbestos in their lungs, then the presence of number of "ferruginous bodies" in the lungs or sputum is no guide to the extent of the disease. Furthermore, pulmonary function studies do not always show good correlation with radiological abnormalities.[40,44] Perhaps more important, neither can be perfectly correlated with the pathologic changes which are eventually discovered by lung biopsy or autopsy. In its early stages, histological diagnosis is unreliable and radiographic evidence to confirm the diagnosis may be entirely missing. The radiological abnormalities have been described in many articles and can be summarized under two headings: changes in pleura and changes in the lungs themselves.

The one common finding in people exposed to asbestos is subsequent calcification of the pleura and the diaphragm. Pleural calcification is often inexplicably unilateral, but autopsies have shown that pleural fibrosis forming characteristic plaques is nearly always bilateral. Because of a different rate of progression on each side, the radiological finding may appear unilateral. These "asbestos" plaques are nearly always in the parietal pleura; yet in spite of quite severe fibrosis, the two layers of the pleura do not always become adherent. A pneumothorax may easily be induced even when

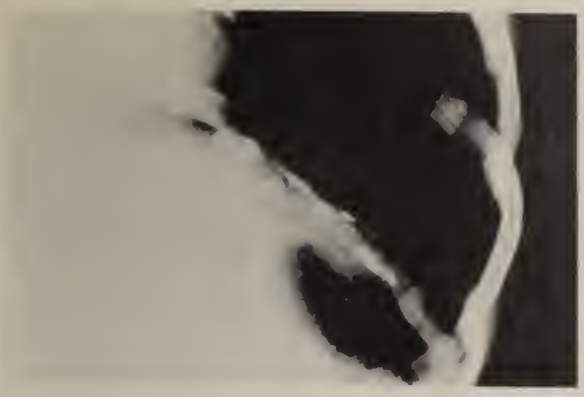

Figure 8.—Calcification in the diaphragm from asbestos. A South African patient.

Figure 9.—Calcification in the diaphragm. A chance finding during a gastrointestinal series on an American with no industrial history.

Figure 10.—Calcification in the diaphragm in a shipyard worker from America.

there are obvious radiological changes which have proceeded as far as calcification (Figure 6). Only in the latest stages do the two layers of the pleura become adherent.

The pattern of calcification is unique for asbestos, resembling a leaf with a rolled and nodular

Figure 11.—Bilateral advanced asbestos calcification.

edge (Figure 7). It can be distinguished from calcification following trauma, either surgical or otherwise. The calcification is most frequent in mid zones and the bases in some geographic areas, where as in others it is infraclavicular as well, spreading throughout the rest of the chest.

Equally diagnostic is calcification on and in the diaphragm. Sections of specimens show calcification actually within the diaphragm at any depth. We do not know of any other circumstance in which similar diaphragmatic calcification occurs except, rarely, following trauma. The diaphragmatic calcification can be unilateral or bilateral and may occur in part of either diaphragm. It may be thick or thin and it seldom affects the movement of the diaphragm until it becomes extensive (Figures 8-10). It is associated with fibrosis in its latest stages but may be seen with an entirely normal lung above it. It is often an unexpected finding, for example, on a routine chest x-ray film (Figure 11). Even before calcification, the diaphragm may thicken, either in short segments or throughout its dome, bilaterally or unilaterally.

The pleura may also thicken to two or three centimeters without calcification. It may resemble fluid on the chest x-ray film, but none may be found (Figure 12). The lungs become encased

Figure 12.—Thickened pleura resembling fluid and encasing the right lung. The right lung is smaller than the left.

and movement is then restricted. As with other changes in asbestosis, the abnormalities may be more extreme on one side than on the other and the thoracic cage may be notably asymmetrical. Almost any combination of these changes occur. The pleura or the diaphragm may be separately affected, there may be calcification or plaque formation, and all or none may be present with or without obvious underlying lung disease.

The reverse is also true: there may be pronounced underlying lung disease without any obvious changes in the pleura or diaphragm. The lung abnormalities may be summarized as a diffuse ground-glass parenchymal fibrosis with a fine stippling. These changes may vary with the type of asbestos and particularly with its mineral content.

An additional feature described for many years is blurring of the cardiac outline, called a "shaggy heart." It also is by no means constant. The pulmonary and cardiac changes are much less reliable and helpful in diagnosis than the pleural and diaphragmatic calcification. There is evidence that the radiological abnormalities increase in number and severity with the length of asbestos exposure, but do not follow any firm rule of progression[42] (Table 1). After this description of the

TABLE 1.[2]—*Radiologic Changes in Asbestos Insulation Workers*

Onset of Exposure (years)	*Number*	*Percent Normal*	*Percent Abnormal*	*Asbestosis Grade:* 1	2	3
40+	121	5.8	94.2	35	51	28
30-39 ...	194	12.9	87.1	102	49	18
20-29 ...	77	27.2	72.8	35	17	4
10-19 ...	379	55.9	44.1	158	9	0
0-9 ...	346	89.6	10.4	36	0	0
TOTALS ..	1,117	51.5	48.5	366	126	50

radiological findings, it should be emphasized that the chest x-ray film may appear to be quite normal even when all other diagnostic findings are significantly abnormal. In searching for a means of early recognition of lung damage it is probable that a combination of pulmonary function testing, supplemented with questionnaires, physical and radiologic examination provides an epidemiologic method suitable for field surveys.

Unfortunately, the laboratory findings are not helpful. The chemical effects of asbestos have been considered by many authors in great detail and much research has been carried out. Chrysotile asbestos is a potent hemolytic agent but other forms of commercially produced asbestos are relatively inactive.[43] Silica, in the particulate form, also has a lytic action on intracellular structures. Asbestos produces no systemic poisoning, and there are no distinctive findings in the blood or in the urine. No minimum lethal dose has been established and there is no evidence of allergy in either occupational groups or experimental animals.

The cause of death in those who have worked with asbestos is usually pulmonary infection. This is usually severe bronchitis and bronchopneumonia, but lobar pneumonia is also common. The patients may die of cardiac failure due to corpulmonale or simply respiratory failure. To these causes must be added the very high incidence of malignant disease.

Pleural Thickening and Calcification

The presence of pleural calcification is significant. It carries with it so many unsolved questions that it is worthy of further comment. It has been thoroughly studied in Finland by Kiviluoto: he compared the chest x-ray films of 6,312 adults living near an asbestos mine with 7,101 chest x-ray films of adults who lived in a similar area but one without an asbestos mine near by.[44] There

TABLE 2.[2]—*Pleural Calcification Among Asbestos Insulation Workers*

Onset of Exposure (years)	Number	Percent Normal	Percent Calcification	Extent of Calcification 1	2	3
40+	121	42	58	37	20	13
30-39	194	65	35	46	15	6
20-29	77	89	10	8	0	0
10-19	379	99	1	5	0	0
0-9	346	100	0	0	0	0
TOTAL ...	1,117					

were 499 cases of pleural calcification among those who lived near an asbestos mine, but there were none in the control series. He called it "endemic pleural asbestos."[44] Selikoff has found pleural calcification in approximately 50 percent of insulation workers with greater than 20 years experience (Table 2).

But even this association is not as simple as it seems. Asbestos has been mined in the town of Shabani in Rhodesia for 60 years. There are large mine dumps of waste material in and around the town. Yet a personal search by one of the authors over a ten year period found no diaphragmatic calcification, pleural plaques or pleural calcification. Three independent radiological surveys of the miners and their families who lived in this area were reviewed by two experienced chest physicians, specially looking for diaphragmatic calcification, pleural plaques and pleural calcification. They found none, even when these surveys were repeated after a period of four years.[45] There was one exception, and it served to underscore the accuracy of the method of the examination. The exception was a miner who had worked for many years in the northwestern Cape of South Africa where pleural calcification is almost a normal finding in the population.[46] It seems likely that other factors relating to the asbestos industry apart from the asbestos itself are significant. MacDonald stated that the factor which causes asbestosis is not the same as that which causes pleural calcification.[47] So far, only an association has been shown and not a proven casual relationship. Nor does the occurrence of unilateral or bilateral calcified plaques imply the presence of an underlying asbestos pneumoniconiosis. It may occur in isolation, but it has been shown that the more severe the degree of the lung changes among asbestos workers, the greater the frequency of pleural calcification.[2]

Exposure to Low Concentrations of Asbestos

To make the diagnosis the possibility of the disease must be constantly borne in mind, even when there are patients who have been exposed to low concentrations of asbestos. The effects of such low concentrations in industry were reported by Murphy and associates in 1971.[32] In surveying 101 pipe coverers engaged in the construction of new ships, they found that asbestosis (using the aforementioned criteria) was 11 times more common in those exposed to low concentration than it was in workers employed in the same shipyard who had no exposure. Even when the concentration of asbestos was low, it was possible to detect asbestosis after 13 years of exposure, and after 20 years the prevalence had reached 38 percent. A very careful history may be required to provide the one vital clue which puts the whole picture together.

Asbestos Carcinogenesis

Finally, the vexing problem of carcinogenesis associated with asbestosis should be considered. There is no doubt that inhaling asbestos fibers carries a considerable carcinogenic risk, not only to the lungs, pleura, peritoneum and larynx[48] but possibly to the oropharynx, pancreas and gastrointestinal tract. Thompson predicted that asbestos will rival cigarettes as a cause of lung cancer in the future, because the production of asbestos has increased 1,000-fold during the last century.[49,50] The long delay period in producing its changes, from 20 to 40 years of exposure, may mean that we are yet to face the onslaught of malignant disease which could result.

But why should asbestos be carcinogenic? One possibility is that asbestos enhances and prolongs the carcinogenic effects of benzpyrene by adsorbing the carcinogen.[51] Some researchers take a different view because animal studies show that the trace metals nickel, chromium, manganese and iron are also carcinogenic agents and are found in asbestos.[52] Stanton took yet another position and reported that the structure of the fibers is responsible for carcinogenicity. He found that fibers between 0.5 and 5 microns in diameter and less than 80 microns in length were the most carcinogenic and suggested that this was the result of a physical irritation rather than a biochemical one.[53] The fact remains that all commercially-used types of asbestos have been shown to be carcinogenic.

Richard Doll reported that the average risk of

TABLE 3[55]—*Mortality Data=623 Asbestos Insulation Workers NY-NJ, January 1, 1943-December 31, 1971. All with 20 or More Years of Exposure to Asbestos*

	1943-1951		1952-1961		1962-1971		TOTAL 1943-1971	
	E	O	E	O	E	O	Expected	Observed
Total cancer	11.3	28	18.3	57	17.6	104	47.2	189
Lung cancer	1.5	13	3.5	23	5.1	48	10.1	84
Pleural mesothelioma	..	1	..	2	..	5	..	8
Peritoneal mesothelioma	..	1	..	3	..	20	..	24
GI	4.1	7	5.0	18	3.9	16	13.0	41
All other sites	5.7	6	9.8	11	8.6	15	24.1	32
Asbestosis	..	1	..	10	..	22	..	33
All other causes	65.1	44	89.4	94	78.3	61	232.8	199
TOTAL ALL CAUSES	76.4	73	107.7	161	95.9	187	280.0	421

Expected rates are based upon age-specific health rate data of U.S. National Office of Vital Statistics from 1949-1967.

carcinoma of the lung among employees who have worked for over 20 years or more in asbestos factories is ten times as high as that of the general population.[54] Selikoff concluded that malignant disease was the most important complication of asbestos exposure and found that 45 percent of New York insulation workers died of cancer.[55,56] In his study of the causes of death for 623 asbestos insulation workers, 84 were shown to have died of lung cancer, whereas the expected number was 10.1.[55,57] There were 42 deaths from mesothelioma, and gastrointestinal malignancies occurred three times the expected rate (Table 3).[55] Selikoff then attempted to assess the effect of smoking and followed 370 of the original group from 1963 to 1967. He found the risk of lung cancer for an asbestos worker who smoked was 92 times greater than for a non-smoker in the general population.[58]

In another study, Selikoff reviewed the histories of 17,800 American and Canadian insulation workers, following them from 1967 until December 1971. In a group this size, 44 deaths from lung cancer would be expected but the actual number proved to be 213. Of those who smoked, approximately 25 percent (134 out of 596) of the deaths were due to lung cancer.[55] Later, the same author tried to exclude the possible effects of other insulation materials by studying death rates for employees in a factory that specifically used asbestos.[59] In this series of 484 deaths, 73 were due to lung cancer, instead of the expected 11.4. There were an additional seven deaths due to mesothelioma and a larger than expected number of gastrointestinal neoplasms. He suggested that the typical latent period for carcinoma of the lung was more than 20 years after the onset of the exposure to asbestos, with a variation in exposure from one day through many years.

This apparently firm conclusion is not straightforward. The people living near or working in the mines around Shabani in Rhodesia (already referred to because of their strange lack of pleural and diaphragmatic calcification) have a similar low incidence of malignancy.[45,46] The control series was provided from a small population in a nearby gold mining town. Osburn reported a high incidence of malignancy in the gold miners in Gwanda but none has occurred in Shabani.[60] The findings are true of both White and African miners and their way of life and the background of all concerned in these two studies are very similar. Thus, for some inexplicable reason, exposure to asbestos in the town of Shabani over a period of many years does not carry an increased risk of malignancy. This same discrepancy has been demonstrated in Canada. A survey by MacDonald[17] of 1,200 asbestos miners in Quebec showed no unusually high rates of mortality from lung cancer. If this series is then examined more closely, it is found that those who were heavily exposed did have an increased rate of lung cancer, as much as five times as high as those who were lightly exposed, but the overall rate for the population was not increased.

A similar problem arises with mesotheliomas. These are tumors of the pleura and the peritoneum and are extremely rare, with an expectancy of about one in 10,000 deaths among the general population.[61] But Selikoff found that 7 percent of deaths among asbestos workers were due to mesotheliomas. Wagner from South Africa reported a series of 33 patients with mesotheliomas, of which 32 had exposure to asbestos.[62] This series needs

care in interpretation, because the area from which these patients were drawn has an extremely high asbestos exposure and it would be difficult to find many members of the population who have not been exposed to this dust. Nevertheless, there is not the slightest doubt that the incidence of mesotheliomas in the Cape Province of South Africa is incredibly high, yet in the Transvaal a few hundred miles to the east a similar high incidence is not found.[63] After sixty years' exposure in Shabani, Rhodesia, there have been no mesotheliomas.[45] An excess of mesotheliomas has not been found in the asbestos mining regions of Canada.[64]

Minimal exposure does not seem to provide protection from mesotheliomas. Newhouse reported 76 patients with mesothelial tumors of which approximately half (53 percent) had a history of either occupational or other asbestos exposure.[65] If they did not work with asbestos themselves they lived with an asbestos worker. Of the patients, 31 percent lived within half a mile of the asbestos factory. Either asbestos fibers or asbestos bodies were found in the lungs of 30 of 38 patients. However, this is near the percentage found in urban populations and its significance must therefore be doubtful. The length of exposure in the series varied from 16 to 55 years, but mesotheliomas have been reported in children aged six years or less. In England, Owen studied 17 patients from Liverpool with mesotheliomas and found that only 11 had a history of handling asbestos and only two worked directly with the material.[66]

Equally uncertain is the role of exposure to asbestos in increasing the risk of malignant disease in other parts of the body, particularly in the stomach, colon and rectum. Selikoff found a two-to-three times increased risk for gastrointestinal cancer in his studies, but a personal investigation by one of the authors in the Cape Province of South Africa did not find any significant increased incidence of malignant disease of the stomach or elsewhere in the alimentary tract. Asbestos exposure has recently been linked with laryngeal carcinoma.[48] It has been suggested that because an asbestos body has been found in the pancreas, this too may be the cause of increased pancreatic carcinoma. However, such isolated cases are of doubtful significance. It is not unreasonable to suspect that asbestos bodies will be found almost anywhere in the tissues of urban populations, if they are sought with sufficient care.

Occupational Standard

The present federal standard for occupational exposure to asbestos dust is five fibers per cubic centimeter greater than 5 microns in length as an eight-hour time-weighted average.[17] By 1976, the Department of Labor will reduce the standard to two fibers per cubic centimeter. Thus, the asbestos worker who typically inhales 6 to 8 million cubic centimeters of air per day will inhale 30 to 40 million asbestos fibers under the present standard, to be reduced to a mere 12 to 16 million under the future standard.[67,68] No one knows whether the two fibers per cubic centimeter standard will protect the occupationally-exposed worker from asbestos related disease.[68] There is still considerable debate concerning the development and implementation of this new standard.[69,70] Moreover, there are numerous fibers less than 5 microns in length (especially less than 1 micron as identified by the electron microscope). These minute fibers, not even mentioned in the occupational standards, are easily inhaled and may be particularly injurious.[71]

Conclusions

The literature on asbestos is so extensive that this survey has only skimmed the surface. However, certain conclusions seem clear.

Asbestos is, indeed, a "lethal dust" and exposure to it carries many and considerable risks. The major risk is of pulmonary fibrosis. That risk is increased many times if the patient is also a smoker. But exposure to asbestos also increases the risk of carcinoma of the lung, and again if the patient smokes this is increased further. It seems probable that exposure to asbestos, particularly in small amounts, increases the likelihood of a mesothelioma developing. A close relationship to the degree of exposure is not firmly established, and why a mesothelioma should develop in some patients while in others a carcinoma of the lung develops is not understood. In some geographical areas, exposure to asbestos carries an increased risk of malignant disease of the alimentary tract, though it is not certain that this is a risk in every locality.

For each of these conclusions, with which most researchers would agree, there remain many unanswered questions. Why do apparently similar mines carry a totally different risk of pleural or malignant disease? Why are calcified pleural plaques unilateral in many cases? How can fibers pass through an apparently normal lung, subse-

quently damage the pleura or the diaphragm, or even pass through both these tissues to irritate the peritoneum? Is there a firm relationship between the amount of pleural fibrosis and the development of mesotheliomas? Is there a positive or a negative correlation?

A statement made about other malignant disease seems particularly applicable to exposure to asbestos: "An individual who develops a malignant process must possess firstly a susceptibility to the specific carcinogenic activity and secondly survive long enough to develop a malignant neoplasm."[72] We also agree that asbestos by itself is probably not the sole cause; possibly some other factor or factors in association with it will be shown to cause the presently inexplicable variation in the malignant diseases of asbestos workers.

The authors have been unable to find any consistent common denominator associated with asbestos. Indeed, we find that we have not really progressed much further than Ramazzini, a physician of Padua, who in 1746 stated "Diseases arise from the offensive quality of the matter which tradesmen handle in the way of their business. Under this head, I reckon the diseases which affect mine diggers and all workmen who work upon minerals."[73]

Medicine may not have progressed in this respect, but civilization undoubtedly has, and unfortunately the problems of asbestos are no longer confined to "mine diggers and those who work upon minerals." We are all at risk and only time will tell what havoc will be wreaked on all, human and animal, who live in this asbestos age.

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Accidental Internal Burns in Children

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—GABRIEL F. TUCKER, JR., MD, *Philadelphia*

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Refer to: Coburn JW, Hartenbower DL, Norman AW: Metabolism and action of the hormone vitamin D—Its relation to diseases of calcium homeostasis (Medical Progress). West J Med 121:22-44, Jul 1974

Medical PROGRESS

Metabolism and Action of the Hormone Vitamin D

Its Relation to Diseases of Calcium Homeostasis

JACK W. COBURN, MD, and DAVID L. HARTENBOWER, MD, *Los Angeles*
ANTHONY W. NORMAN, PhD, *Riverside*

Extensive experimental evidence has established a significant role of calciferol in the maintenance of normal calcium homeostasis. Present knowledge indicates that vitamin D_3 must first be converted to 25-OH-D_3 and then to 1,25-$(OH)_2D_3$, the most active known form of the steroid. Many of the factors regulating the rate of production of this last steroid from its precurser have been evaluated, and the concept that vitamin D functions as a steroid hormone seems to be well established.

Deranged action of calciferol, caused by impaired metabolism of the steroid or through altered sensitivity of target tissues, may be involved in the pathophysiology of several disease states with abnormal calcium metabolism.

It is noted that liver disease, osteomalacia due to anticonvulsant therapy, chronic renal failure, hypophosphatemic rickets, hypoparathyroidism, hyperparathyroidism, sarcoidosis and idiopathic hypercalciuria have possible relation to alterations in metabolism or action of vitamin D.

The future clinical availability of 1,25$(OH)_2D_3$ and other analogs of this steroid may offer potential therapeutic benefit in the treatment of certain of the disease entities discussed.

THREE OF THE MOST IMPORTANT of the biological regulators of calcium and phosphorus metabolism are vitamin D (calciferol), parathyroid hormone (PTH) and calcitonin. Significant developments and advances have been made in recent years concerning each of these controlling factors. It is likely that calciferol, which may be classified chemically as a steroid, acts in a manner similar to that of well-known steroid hormones, such as estrogen, aldosterone, testosterone and hydrocortisone. Also, there is now evidence to support the thesis that the active form of calciferol is a steroid hormone which is produced by the kidney in response to various physiological signals. With this perspective in mind, it is possible to identify new relationships between vitamin D, in reality a hormone, its secretory organ (the kidney), the target tissues (the intestine and skeleton) and various disease states related to calcium homeostasis and vitamin D.

From the Medical and Research Services, VA Wadsworth Hospital Center, Los Angeles, the Department of Medicine, UCLA School of Medicine, and the Department of Biochemistry, University of California, Riverside.

Some of the work reported herein has been supported by USPHS Grants AM 14750 and AM 09012 and Contract PH-43-68-1040.

Reprint requests to: J. W. Coburn, MD, Nephrology Section 691/111L, VA Wadsworth Hospital Center, Los Angeles, CA 90073.

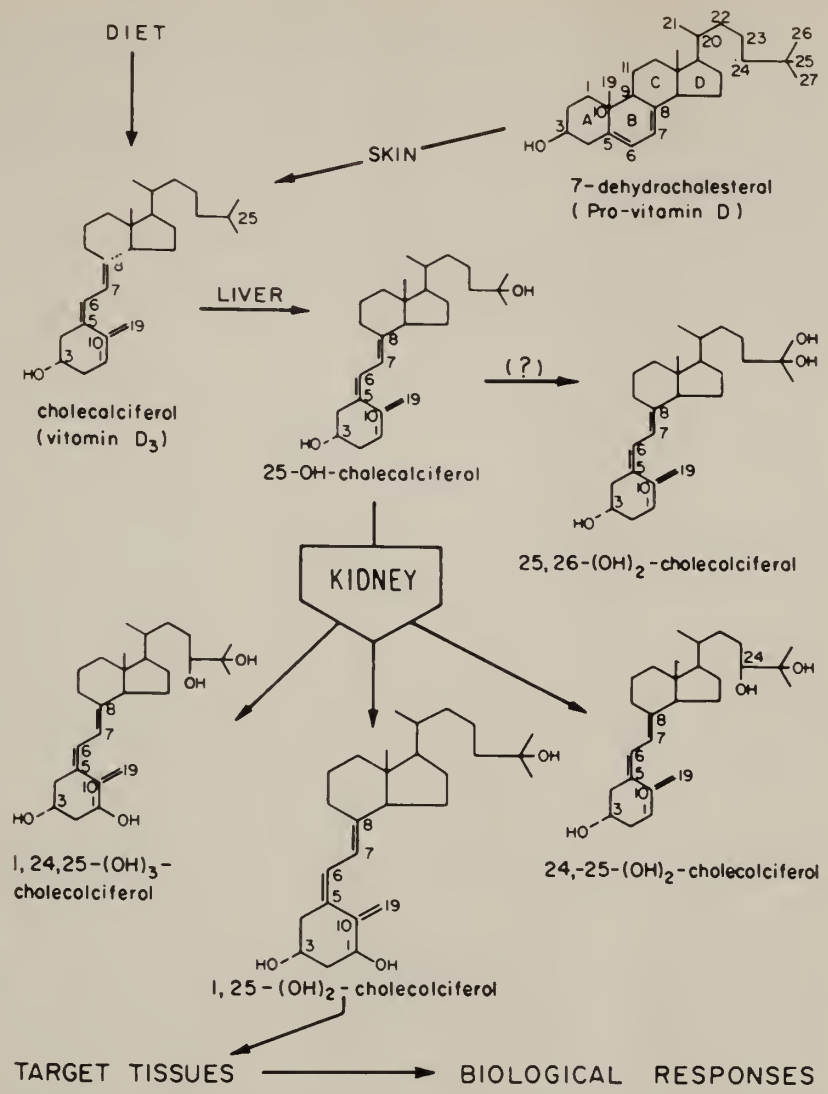

Chart 1.—Schema of vitamin D metabolism. The contribution of 25,26-$(OH)_2$-cholecalciferol,[19] 24,25 $(OH)_2$-cholecalciferol,[18] and 1,24, 25$(OH)_3$-cholecalciferol[20] to calcium homeostasis is uncertain.

The preparation of suitable radioactively-labelled calciferol compounds has permitted the biochemist to unravel many of the complexities of the mechanism of vitamin D action and has allowed study of the fate of physiological doses of vitamin D.[1-3] Thus, radioactivity has been detected following the administration of labelled cholecalciferol in esters of vitamin D,[4] in bile acids[5] and, most significantly, in more polar metabolites of vitamin D.[6]

Extensive studies carried out in a number of laboratories indicate that vitamin D_3 (cholecalciferol) undergoes obligatory two-step metabolism for production of the biologically active form, 1,25-dihydroxy-vitamin D_3 (1,25$[OH]_2D_3$). The first metabolic step occurs in the microsomal fraction of liver cells, where D_3 is hydroxylated at the 25 position.[7-9] One of the most important recent developments has been the appreciation that the production of 1,25$(OH)_2D_3$ occurs in the kidney. This was first demonstrated by Fraser and Kodicek[10] and quickly confirmed by Norman et al[11] and Gray et al.[12] This latter metabolic conversion has been shown to occur in the mitochondrial portion of the renal cortical cells.[13] In addition to 25-hydroxy-vitamin D_3(25-OH-D_3)[14] and 1,25$(OH)_2$-D_3,[15-17] several other metabolites of vitamin D have been characterized to date. These include 24,25-dihydroxycholecalciferol,[18] 25,26-dihydroxycholecalciferol[19] and 1,24,25-trihydroxycholecalciferol.[20] These developments are summarized in Chart 1.

When physiological doses of radioactive vitamin D_3 were given to rachitic chicks, it was found that the parent steroid was converted to more polar metabolites.[21] Furthermore, the relative

TABLE 1.—*Quantitative Considerations of Calciferol and its Metabolites*

	Vitamin D_3+metabolites			*Vitamin D_2+metabolites*		
	D_3	*25-OH-D_3*	*1,25(HO)$_2D_3$*	*D_2*	*25-OH-D_2*	*1-25(OH)$_2D_2$*
Molecular weight	384.6	400.3	416.3	396.6	412.4	428.0
ng/65 pmoles*	25.00	26.01	27.06	25.78	26.80	27.8
"Units"/μg	40.0	38.5	37.0	38.8	37.3	35.8

*1.0 International unit (IU) of vitamin D_3 (cholecalciferol) has been defined to be 0.023 μg (65.0 pmoles).[23] No official definitions of "units" have been formulated for 25-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol.
Some problems related to quantitation of vitamin D are discussed elsewhere.[24] In this presentation 1.0 "unit" (U) of 25-hydroxy-vitamin D_3 and 1,25-dihydroxy-vitamin D_3 is defined to be 65.0 pmoles.

proportions of these more polar steroids varied in different tissues. In plasma, 25-OH-D_3 was the predominant form, while in the intestine, 1,25-(OH)$_2D_3$ was the major component of calciferol present. In the skeleton, D_3, 25-OH-D_3 and 1,25-(OH)$_2D_3$ were each present in substantial amounts with somewhat greater quantities of 25-OH-D_3.

The quantitative interrelationships between the parent vitamin D and its metabolites are summarized in Table 1. Most studies of vitamin D metabolism have utilized cholecalciferol or vitamin D_3, the naturally occurring form. However, ergocalciferol (vitamin D_2), a sterol not naturally occurring in animals, is the form of vitamin D used as a supplement in foods and prescribed by the clinician for various indications.

Identification of metabolites of vitamin D has generally been accomplished in biologic specimens by chromatography of lipid-extracted material obtained some time after the administration of a radioactive form of vitamin D to the experimental animal. One problem with this method has been uncertainty whether a single chromatographic peak contains only one or several closely related compounds. For example, the chromatographic peak that contains 1,25(OH)$_2D_3$ includes only this steroid when lipids from intestinal mucosa are chromatographed, while a similar chromatographic peak from plasma lipids contains 1,25(OH)$_2D_3$ plus one or more additional calciferol steroids.[22]

Moreover, these methods do not provide quantitative information unless the precise amounts of unlabelled vitamin D and its metabolites can be measured in plasma and other tissues. At present, this information can be estimated only in a vitamin D-deficient state. The development of methods for accurately measuring the minute quantities of unlabelled calciferol and its various metabolites that exist in plasma and tissues of man and experimental animals that are not vitamin D-deficient will greatly facilitate the investigation of calciferol metabolism.

TABLE 2.—*Relative Biological Effectiveness of D_3, 25-OH-D_3 and 1,25(OH)$_2D_3$*

Biological Response	*Species*		*Relative Activity**	
			25-OH-D_3	*1,25(OH)$_2D_3$*
Intestinal Ca^{2+} Transport	Chick	1.0	2.0	13-15
Bone Ca^{2+} Mobilization	Chick	1.0	1.5	5-6
Rat Line Test	Rat	1.0	1.4	2-3
Percent Bone Ash	Chick	1.0	1.6	2
Body Growth	Chick	1.0	1.0	5

In each instance the response obtained by vitamin D_3 was set equal to 1.0 and the responses obtained from an equal molar quantity of the other vitamin D metabolites calculated accordingly. See references 24, 26, 28.

As a consequence of work carried out by a number of investigators, it has been possible to isolate and purify several metabolites of the parent vitamin D. Noteworthy in this respect were the efforts necessary to isolate and chemically characterize 1,25(OH)$_2D_3$. This metabolite possessed several characteristics which justified the substantial efforts required for its isolation and chemical characterization:[55] (a) it was localized mainly in the intestine, a target tissue for vitamin D, but not in presumed non-target tissues, such as the liver; (b) it was the predominant form of vitamin D_3 found in the chick intestine after the administration of a physiological dose; (c) it had biological activity greater than D_3; (d) there were selective and finite binding sites in the cell nuclei of target tissues; and (e) its appearance in the intestine and intestinal chromatin coincided with an increase in the intestinal transport of calcium. These results support the contention that 1,25(OH)$_2D_3$ is the compound responsible for physiological actions characteristic of calciferol.

With the realization that the kidney is the organ which produces 1,25(OH)$_2D_3$ from its precursor, 25-OH-D_3, it was possible to prepare small quantities of the steroid by repetitive in-

cubation of radioactive 25-OH-D_3 with homogenates of kidney tissue from vitamin D-deficient chickens.[11] Extraction and extensive chromatography of the incubation media yielded adequate amounts of the pure metabolite to permit its analysis by mass spectrometry. These results supported identification of the compound as 1,25-$(OH)_2D_3$. The molecular weight of 416 is consistent with the addition of one oxygen atom to the parent molecule, 25-OH-D_3, which has a molecular weight of 400. Additionally, it was known from other experiments that tritium was specifically lost from the number 1 carbon position with the conversion of 1,2-^{3}H- and 4-^{14}C-labelled cholecalciferol to 1,25$(OH)_2D_3$.[16]

With the determination of the chemical structure of 1,25$(OH)_2D_3$ and the ability to produce this steroid by the enzymatic incubation of 25-OH-D_3 with kidney mitochondria, it has been possible to evaluate the biological activity of 1,25-$(OH)_2D_3$ in certain experimental animals. A summary of these results is given in Table 2. Thus, a single dose of 1,25$(OH)_2D_3$ is 13 to 15 times as effective as D_3 in stimulating the intestinal absorption of calcium and 5 to 6 times as effective as D_3 in elevating the serum calcium level.[26,27] In experiments where 1,25$(OH)_2D_3$ was administered daily, it is equally if not more active than vitamin D_3 compared with other criteria tested (bone ash, serum calcium levels and rate of growth).[27,28] Although the results obtained to date are not highly quantitative, they support the contention that 1,25$(OH)_2D_3$ is the most highly biologically-active natural form of D_3 presently known.[28-30] There is the prospect that this steroid may be capable of meeting all the nutritional requirements provided by D_3; however, this cannot be critically tested until a greater supply of 1,25$(OH)_2D_3$ is available. As is described later, it is possible that 1,25$(OH)_2D_3$ may have therapeutic uses in certain clinical disorders associated with altered metabolism of vitamin D or impaired production of 1,25-$(OH)_2D_3$.

Mechanism of Vitamin D Action

A characteristic feature of the biological response to the administration of D_3 is the lapse of time required before an increase in calcium transport occurs. When a vitamin D deficient animal is given either a physiological quantity (50 IU) or a very large dose (500 to 5000 IU) of D_3 there is a delay of up to 30 to 50 hours before

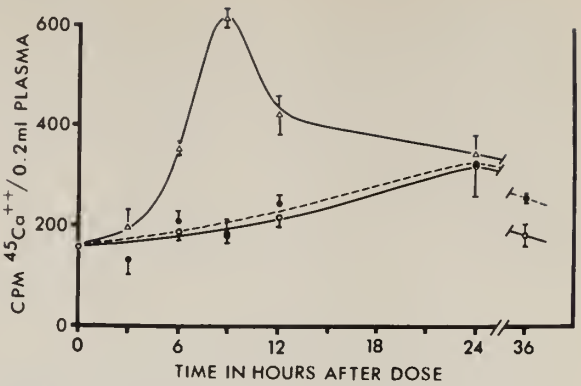

Chart 2.—The appearance of radiocalcium (^{45}Ca) in plasma of chicks following its intraduodenal administration. This study of intestinal absorption was carried out at varying intervals after the administration of vitamin D_3 (open circles), 25 hydroxycholecalciferol (closed circles), and 1,25 dihydroxycholecalciferol (open triangles). The former two were given in doses of 5-U while 1.8U of the latter was given. Reprinted from Myrtle and Norman with permission.[26] Copyright 1971 by the American Association for the Advancement of Science.

intestinal calcium transport is maximally stimulated. Originally, three possible explanations for this time lag were postulated:[31] A time-dependent requirement for (a) the uptake and localization of calciferol in the intestine, (b) the metabolism of calciferol to new compounds; and/or (c) induction of the synthesis of new proteins which then participate in or facilitate the appearance of the biological response. It is now known that this delay is related to the requirement for conversion of D_3 to 1,25$(OH)_2D_3$ and to the action of this latter sterol in transmitting new genetic information necessary for the biological response. The time lag for a response in intestinal calcium transport was not shortened appreciably when 25-OH-D_3 was given. However, when 1,25$(OH)_2D_3$ was administered, a time delay was shortened to 8 to 12 hours before the maximal stimulation of intestinal calcium transport.[26,30,32] These relationships are shown in Chart 2.

Of paramount importance in understanding the mechanism of action of D_3 are the events which transpire between the appearance of 1,25$(OH)_2$-D_3 in the intestinal mucosa and the maximum stimulation of calcium transport. The administration of D_3 to vitamin D-deficient chicks, rats and other species is followed by the appearance of a calcium-binding protein (CaBP)[33,34] and an increase in activity of alkaline phosphatase[35] in intestinal mucosa. Although the exact roles of these substances in calciferol-mediated calcium

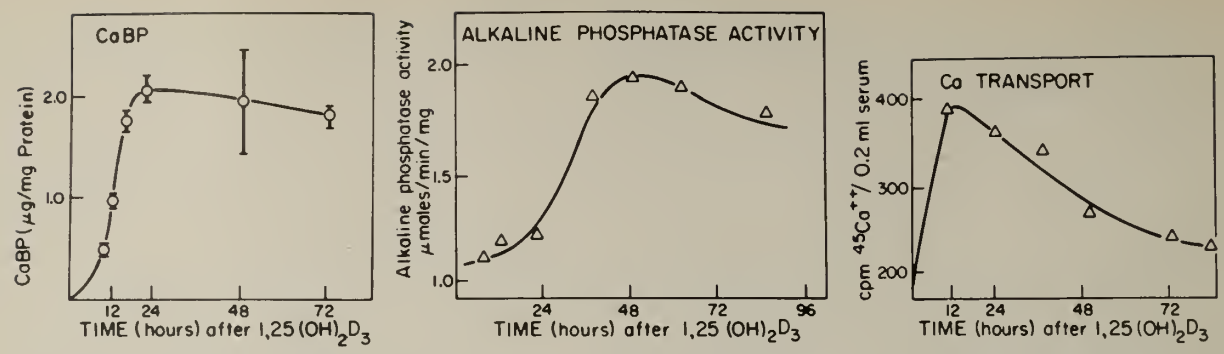

Chart 3.—The relation between the appearance of intestinal calcium binding protein (CaBP) and alkaline phosphatase activity and the stimulation of intestinal calcium transport at varying intervals after the administration of $1,25(OH)_2D_3$. Intestinal calcium transport was assessed as in Chart 2.

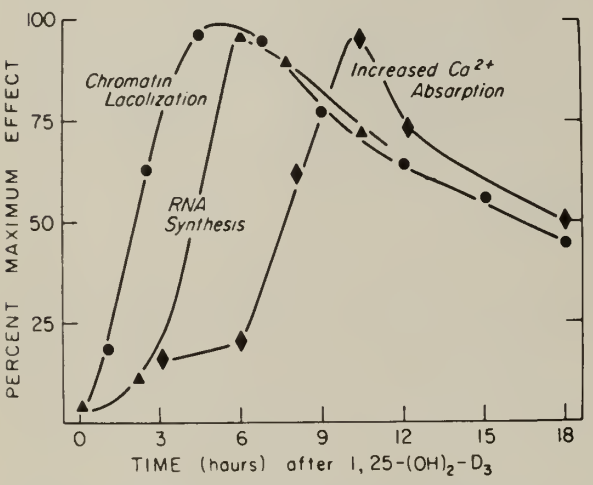

Chart 4.—Sequence of events which occur in the intestinal mucosa after the administration of $1,25(OH)_2D_3$. Either radioactive or non-radioactive $1,25(OH)_2D_3$ (325 pmoles) were given to separate groups of rachitic chicks. Localization of $1,25(OH)_2D_3$ in the intestinal chromatin, stimulation of pulse labeling by RNA by ^{3}H-uridine and stimulation of the intestinal absorption of Ca^{2+} are shown as the percent of the maximum observable effect. Reprinted from Tsai and Norman with permission.[211]

transport are not definitely known, their appearances are dependent upon the administration of D_3 and are highly characteristic of a calciferol-response. Also, it has been shown that both the production of the CaBP and the increase in alkaline phosphatase activity are not elicited by the parent D_3 but are produced in response to $1,25(OH)_2D_3$.[36] In addition, the time course of appearance of CaBP coincides with the appearance of augmented intestinal calcium transport after the administration of $1,25(OH)_2D_3$. However, high levels of CaBP persist at 24 to 48 hours, when the calcium transport response to $1,25(OH)_2D_3$ has diminished (Chart 3). Since the CaBP was measured by an immunoassay, it is not known whether the immunoreactive substance present at 24 to 48 hours is also active in terms of binding calcium. The increased alkaline phosphatase activity that follows the administration of $1,25(OH)_2D_3$ persists beyond the augmentation of intestinal calcium transport, supporting the view that alkaline phosphatase does not play a rate-limiting rôle in the transport of calcium.[36] The reasons for a decrease in calcium transport 24 to 48 hours after the administration of $1,25(OH)_2D_3$ are not entirely clear. A study of the turnover time of intestinal mucosal cells in both vitamin D-deficient and vitamin D-repleted chicks reveals complete turnover after 90 to 96 hours in both groups.[36] These observations suggest that the intestinal responses to $1,25(OH)_2D_3$ are capable of being modulated independent of the turnover of the intestinal mucosal cells. Undoubtedly, there is a delicate balance between biosynthesis and biodegradation of critical components involved in the complex system of calcium transport.

A current working hypothesis of the mode of action of $1,25(OH)_2D_3$ in eliciting its characteristic increase of intestinal calcium transport is that the steroid first becomes bound to a protein receptor in the cytoplasm of the intestinal cell. Next, the cytoplasmic receptor and $1,25(OH)_2D_3$ may become bound to the chromatin fraction of the cell nucleus where an undefined series of steps is initiated leading to increased synthesis of messenger ribonucleic acid (RNA) and protein.[37-39] Thus, present data suggest that the association of $1,25(OH)_2D_3$ with a stereospecific receptor of the chromatin fraction of the intestinal cell nucleus precedes the stimulation of its physiological responses (Chart 4).[25] The magnitude of the dose required to saturate these binding sites in intestinal chromatin was similar to the quantity

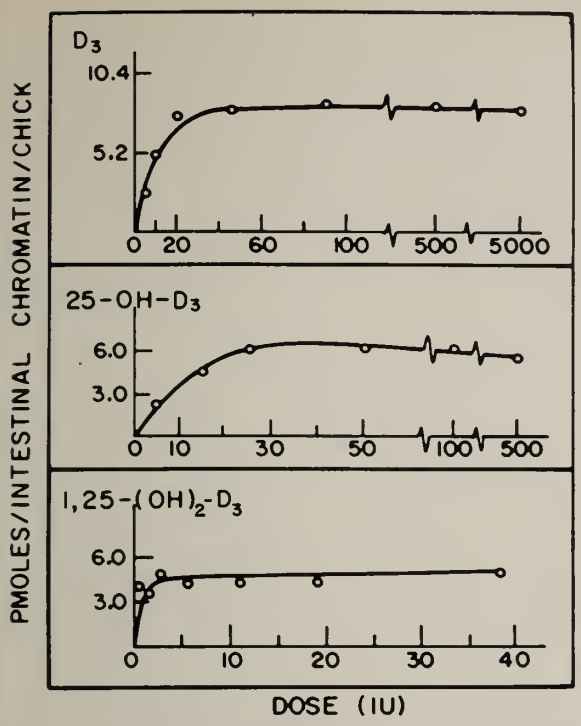

Chart 5.—Relationship between the doses of vitamin D_3, 25-OH-D_3 and 1,25$(OH)_2D_3$ and the quantity of calciferol metabolite present in the intestinal chromatin. One unit represents 65 pmoles (see text).

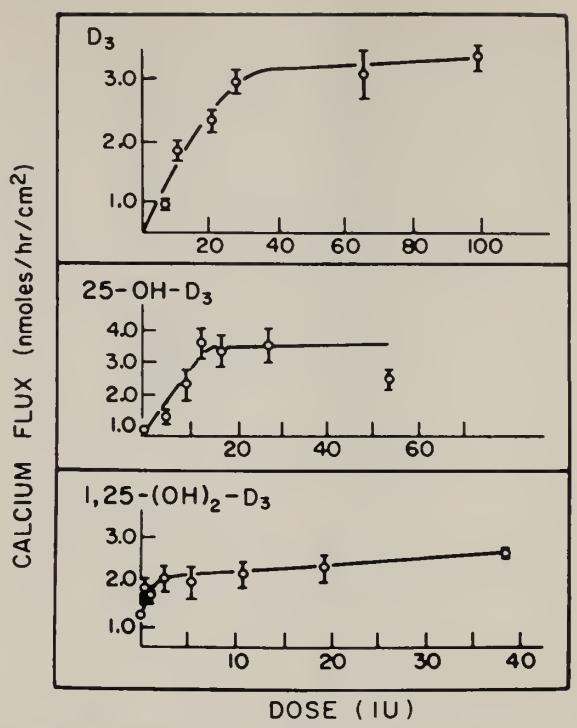

Chart 6.—Relation between the doses of vitamin D_3, 25-OH-D_3 and 1,25$(OH)_2$-D_3 and the magnitude of intestinal calcium transport, measured as flux, serosa to mucosa, in vitro. One unit represents 65 pmoles.

required to produce a maximum increment in intestinal absorption of calcium.[39] Also, the time required for maximal nuclear localization of 1,25-$(OH)_2D_3$ is similar to that expected in view of the time required for the metabolic transformations of D_3 and 25-OH-D_3. It had been shown that actinomycin D, an inhibitor of deoxyribonucleic acid (DNA) directed RNA synthesis, was able to block the response to D_3[40-42] and similar results have been obtained with 1,25$(OH)_2D_3$.[43] These results support the concept that 1,25-$(OH)_2D_3$ activates or stimulates the biochemical expression of genetic information which induces the biosynthesis of new proteins or alters membrane structure in a manner necessary for the transcellular movement of calcium.

In this respect, the mode of action of calciferol may be similar to that proposed for other steroid hormones, testosterone, aldosterone, estrogen, and progesterone. A major concept to be emphasized is that 1,25$(OH)_2D_3$ is, in reality, a steroid hormone produced by the kidney. Concerning the mode of hormone action, it has been possible to show that the localization of radioactivity in the intestinal mucosal chromatin after the administration of radioactively labelled D_3 is specific for 1,25$(OH)_2D_3$. Thus, experiments were carried out to study saturation of binding sites in the nucleus of the target intestine.[39] There were similar maximal amounts of 1,25$(OH)_2D_3$ bound to the chromatin fraction when increasing doses of either radioactive D_3, 25-OH-D_3, or 1,25$(OH)_2$-D_3 were administered to vitamin D-deficient chicks (Chart 5). Also, the doses of D_3, 25-OH-D_3 or 1,25$(OH)_2D_3$ required to saturate chromatin binding sites with 1,25$(OH)_2D_3$ were similar to the quantities of each steroid needed for maximal stimulation of intestinal transport of calcium (Chart 6). This correlation between the quantity of steroid necessary to saturate the intestinal chromatin receptor and that required to produce a maximum stimulation of intestinal calcium transport provides strong evidence for the importance of chromatin binding of 1,25$(OH)_2D_3$ in the ultimate appearance of the biological response to vitamin D. A schematic representation of the sequence of events whereby vitamin D leads to increased intestinal transport of calcium is shown in Chart 7.

The skeleton is also an important site of vitamin D action; and there is general agreement that calciferol promotes resorption of bone[44,45] and

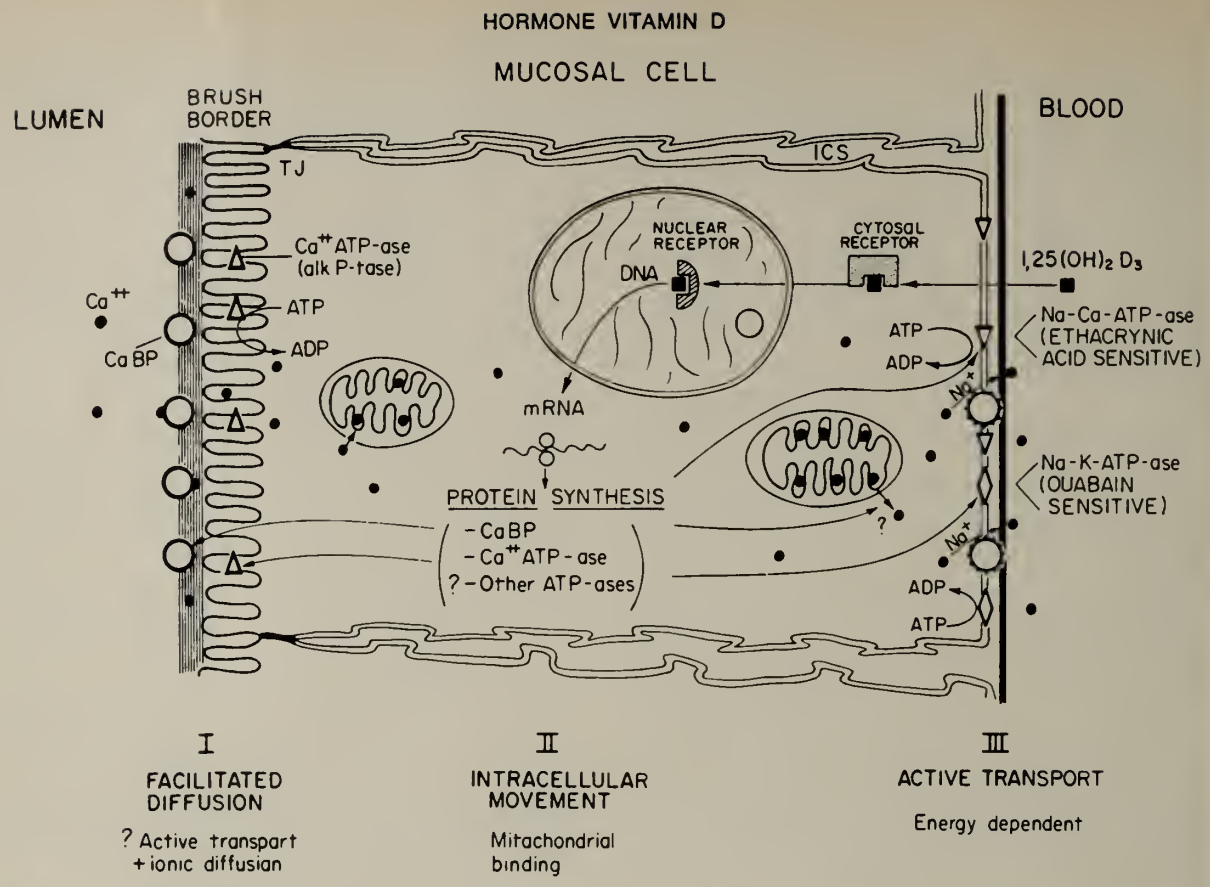

Chart. 7—A schematic representation of events currently believed to be involved in the transport of calcium across the intestinal cell. Abbreviations include: CaBP, calcium-binding protein; TJ, tight-junction; and ICS, intercellular space. Reprinted from Coburn, Hartenbower and Massry.[212]

leads to calcium mobilization. Both 25-OH-D_3 and $1,25(OH)_2D_3$ are capable of stimulating bone resorption in tissue culture[46] and *in vivo*.[47] However, $1,25(OH)_2D_3$ is 100 to 300 times more potent in eliciting this response than 25-OH-D_3, while D_3 is without effect *in vitro* (Chart 8). In a study of the time course of appearance of $1,25(OH)_2D_3$ in skeletal tissue,[39,44] maximal localization of $1,25(OH)_2D_3$ occurred within two to four hours, somewhat more rapidly than its appearance in the intestine.

The mechanism whereby calciferol produces normal mineralization of osteoid in the skeleton (for example, the healing of rickets or osteomalacia) remains uncertain. One view is that calcification of osteoid occurs because the steroid leads to normal concentrations of calcium and phosphate in the extracellular fluid surrounding the osteoid. Another concept is that calciferol may alter osteoid and render it susceptible to normal calcification. The latter view is supported by the clinical observation that healing of rickets may occur while serum calcium and phosphorus levels remain low or even fall.[48,49] From histochemical observations, it has been suggested that calciferol is necessary to produce a "calcification-front" along areas of new mineralization.[50] With an elevation of serum calcium and phosphorus in the absence of vitamin D, such a calcification front fails to appear.[51]

Little is known of the biochemical details of the skeletal response to $1,25(OH)_2D_3$. There is localization of $1,25(OH)_2D_3$ in nuclei of bone cells[52] and, actinomycin D, an inhibitor of DNA directed RNA synthesis, can block vitamin D_3-mediated calcium mobilization from bone.[53,54] At present, the limited data available suggest that the mode of action of $1,25(OH)_2D_3$ in the skeleton is similar to its action in the intestine. However, this concept requires documentation by direct experimentation. As can be appreciated, the design of appropriate studies in skeletal tissue offers particular challenges to the ingenuity of the investigator.

One new view proposes a possible role of vitamin D in the metabolism of bone collagen. Simply speaking, the matrix which provides the framework for normal skeletal calcification is

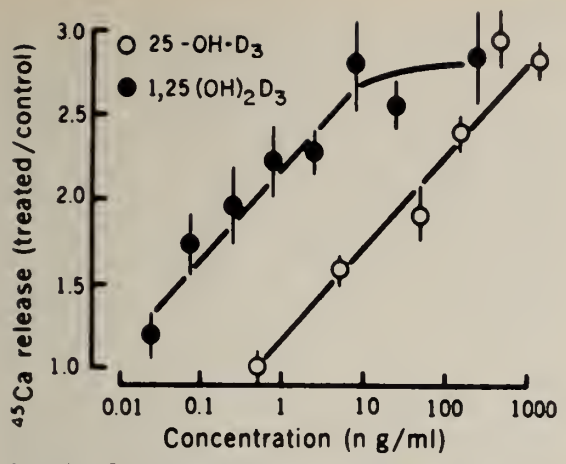

Chart 8.—Comparison of in vitro release of ^{45}Ca from fetal rat bones to various concentrations of 1,25-dihydroxycholecalciferol ($1,25(OH)_2$-D_3) and 25-hydroxycholecalciferol (25-OH-D_3). Points indicate the mean values and vertical lines one standard error for the ratio between treated and control cultures of bone (from Raisz, et al,[47] with permission). Copyright 1972 by the American Association for the Advancement of Science.

made up of collagen fibrils, and it has been reported that vitamin D deficiency leads to a defective quantitative relationship in the cross-linkages between the chains of collagen.[55] With maturation of collagen, the normal development in cross-linking between newly formed collagen fibrils may precede calcification,[56] and defective mineralization could occur because of altered collagen synthesis in vitamin D deficiency.[57] These suggestions are speculative, but they provide a possible biochemical basis for the abnormal skeletal mineralization occurring in the absence of vitamin D.

A third possible target organ for the action of vitamin D is the kidney. Various workers have proposed that vitamin D or its metabolites can enhance the tubular reabsorption of phosphate.[58-60] Such effects cannot always be shown,[61,62] and it is uncertain whether this action is of physiologic significance or represents a pharmacologic response. The administration of large doses of vitamin D is almost always associated with an increase in urinary calcium.[63-65] Under such conditions, the intestinal absorption of calcium is increased, bone resorption may be augmented and the level of serum calcium may rise, thereby increasing the filtered load of calcium and causing suppression of parathyroid activity; the result would be augmented urinary calcium excretion. It has been suggested that large doses of vitamin D may directly inhibit calcium transport by the nephron,[65] but Bernstein, Kleeman and Maxwell[66] did not find such an action. Moreover, Ney, Kelly and Bartter[67] found that urinary calcium excretion actually fell during the first two to 25 hours after the administration of vitamin D to rachitic dogs while serum calcium was unchanged; six days later, when serum calcium levels were higher, urinary calcium had increased.

These observations suggest that vitamin D may enhance the tubular reabsorption of calcium, but such an effect could be obscured as serum calcium rises. Puschett et al found that large doses of vitamin D and smaller quantities of 25-OH-D_3 enhanced the tubular reabsorption of calcium.[60] The mechanisms whereby vitamin D or its metabolites act on the kidney are obscure. However, it should be noted that a vitamin D-sensitive, calcium-binding protein, which is immunologically similar to that found in the intestine, has been found in renal tubular cells.[68]

Regulation of the Metabolism of Vitamin D

Under natural circumstances, vitamin D_3 is produced in the skin by the photochemical irradiation of its precursor, 7-dehydrocholesterol, a compound present in abundant quantities in the sublayers of the epidermis. In the event that this photochemical reaction is restricted, the diet can provide an alternate source of vitamin D. Whatever its source, vitamin D is subjected to a remarkable series of metabolic transformations: First, vitamin D_3 is transported to the liver where it is hydroxylated to 25-OH-D_3 by a microsomal enzyme via a cytochrome P-450-mediated reaction.[71] Bhattacharyya and DeLuca[69] state, on the basis of data obtained in rats, that this metabolic transformation is subject to regulation. Thus, rats which have received abundant dietary quantities of vitamin D_3 will not convert the same proportion of calciferol to 25-OH-D_3 as animals that have not received D_3. In contrast, Tucker et al,[70] who used chicks as experimental models, could not demonstrate regulation of the conversion of D_3 to 25-OH-D_3 when the dietary intake of D_3 was varied within the physiologic range.

Available observations in man are less certain because it is impossible to be confident about the quantities of D_3 ingested or produced in the skin. Mawer and co-workers[71] report that a greater fraction of vitamin D is converted to a polar metabolite, believed to be 25-OH-D_3, in patients with vitamin D deficiencies than in those who had received substantial quantities of vitamin D.

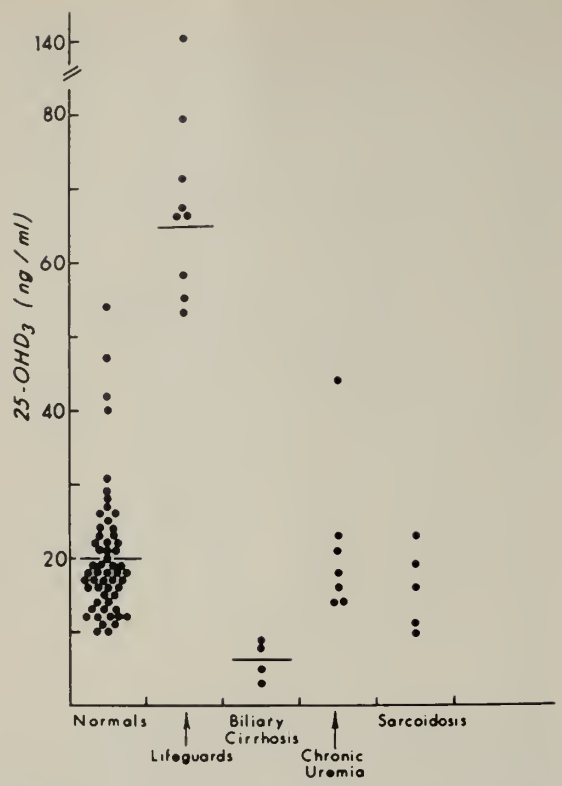

Chart 9.—Plasma levels of 25-hydroxycholecalciferol in normal subjects and those with a variety of clinical conditions. Those with uremia and biliary cirrhosis were receiving varied supplements of vitamin D (from Avioli and Haddad,[73] with permission).

Increased plasma levels of 25-OH-D_3, as measured by a steroid displacement binding assay, were found in patients receiving large quantities of vitamin D or exposed to excessive sunlight (Chart 9).[72,73] These data imply that a certain amount of added vitamin D was converted to 25-OH-D_3.

After hydroxylation by the liver, 25-OH-D_3 is transported to the kidney, where it undergoes a second hydroxylation to $1,25(OH)_2D_3$. This enzyme system is localized exclusively in the mitochondrial fraction of the renal cortex[13] and is inhibited by carbon monoxide, suggesting that it too is a cytochrome P-450 mediated reaction. Estimates of normal plasma levels of D_3[74] and 25-OH-D_3[75] have been reported, and studies of the turnover of cholecalciferol and its metabolites have been made following the injection of radioactive tracers.[76] From such observations, the approximate rates of turnover and plasma concentrations of cholecalciferol and its active products can be calculated;[77] these data are summarized in Table 3.

It is thus possible to calculate the approximate

TABLE 3.—*Plasma Concentrations and Turnover Times in Man of Calciferol and its Metabolites*

	Cholecalciferol	*25-OH-Cholecalciferol*	*1,25(OH)₂-Cholecalciferol*
Turnover time (T½)			
D-deficient (days).	4.5†	16†	1-10‡
Normal (days) ...	4.5	31	....
Metabolite concentrations			
pg*/ml	25,000§	25,000¶	10-100**,††
pmoles/liter	65,000	62,000	24-240
pmoles/ml	65	62	0.024-0.24
units/ml	1	1	$0.38\text{-}3.8\times10^{-3}$

*pg = picogram; 1 pg = 10^{-12}; 1 μg = 1000ng = 10^6 pg.
†Mawer, et al[71]
‡Estimated by authors from unpublished experiments employing $1,25(OH)_2$-^{3}H-cholecalciferol
§Belsey, et al[74]
¶Haddad and Chyu[75]
**Calculated from the data of Mawer et al[141]
††Wong[27] found 0.4 pmoles per ml of $1,25(OH)_2$-cholecalciferol in plasma from D-deficient chicks

ratios of 25-OH-D_3 to $1,25(OH)_2D_3$ and D_3 to $1,25(OH)_2D_3$ circulating in the plasma of man; the ratios in both instances fall in the range of 300 to 3,000. This emphasizes the exceedingly low circulating concentrations of $1,25(OH)_2D_3$ and highlights its impressive biological activity. Indeed, it seems essential that a receptor for $1,25(OH)_2D_3$ in the target intestine or bone must have a very high affinity for the steroid since it circulates in such low concentrations.

Recent observations in several laboratories suggest the intriguing possibility that the activity of 25-OH-D_3-1-hydroxylase, the enzyme converting 25-OH-D_3 to $1,25(OH)_2D_3$ in renal tissue, is subject to regulation, so that the enzyme activity is directly proportional to the calcium needs of the organism. A variety of somewhat conflicting reports have indicated that the activity of the enzyme may be regulated by variations in dietary calcium,[78] serum calcium,[79] activity of parathyroid hormone,[80-83] levels of calcitonin,[84] or the concentration of inorganic phosphate in renal tissue.[85] At present, it is uncertain whether each or all of these factors are operative under physiological circumstances. The regulation of the renal production of $1,25(OH)_2$-D_3 has been studied in the whole animal, where the presence or absence of various hormones is controlled by surgical removal of a specific endocrine gland and blood levels of calcium and phosphorus are regulated by altering their quantities in the diet. It has been reported that dietary calcium[78,80] and phosphorus[85] each may affect circulating levels of $1,25(OH)_2D_3$ and $24,25$-$(OH)_2D_3$. Chicks with the parathyroid removed have been reported to have less $1,25(OH)_2D_3$

than controls, and it has been suggested that parathyroid hormone is a tropic hormone for the production of $1,25(OH)_2D_3$.[80,83] However, the results have not agreed completely with those from experiments undertaken in intact animals, and MacIntyre and associates reported inhibition of $1,25(OH)_2D_3$ production by large quantities of parathyroid extract and stimulation by calcitonin.[81,84] Furthermore, it has been suggested that PTH may exert its effect on the renal production of $1,25(OH)_2D_3$ by altering the intracellular concentrations of phosphate.[87] However, other investigators have not found alterations in vitamin D metabolism with wide variations in phosphate intake.[88]

The problem of regulation has also been approached at a lower level of organization with study of the metabolism of 25-OH-D_3 in preparations of isolated kidney tubules. Using such a method, Shain[89] was unable to demonstrate a stimulatory effect by PTH on the production of $1,25(OH)_2D_3$, while Rasmussen et al[82] reported a stimulatory effect by both PTH and cyclic adenosine monophosphate (AMP). The fact that the responsible enzyme, 25-OH-D_3-1-hydroxylase, is found in the mitochondrial fraction of the cell[13] imposes certain severe restrictions on methods which can be used for detecting the biochemical mechanism by which this enzymatic activity is regulated. Thus, both the cell and the investigator are faced with the transmission of some signal from the surface of the kidney cell to the mitochondrion. This could occur through changes in the intracellular or intramitochondrial pools of either calcium or phosphate. Additionally, one should consider a possible involvement of cyclic AMP. An elevation or diminution of enzymatic activity could be accomplished by changes in either the biosynthesis or biodegradation of the enzyme or simply by activation or inhibition of the existing enzyme system. As a consequence of such successive steps, there would be either increased or decreased production of $1,25(OH)_2$-D_3, the biologically active form of vitamin D.

Another aspect of the renal production of the $1,25(OH)_2D_3$ has been the study of the phylogenetic distribution of this enzyme activity.[90] In an extensive study of the distribution of the renal 25-OH-D_3-1-hydroxylase, it has been found in species of mammalia, including primates, aves, reptilia, amphibia and osteichthyes. When renal tissue from rachitic birds or vitamin D-deficient mammals was used, enzyme levels were much higher, confirming previous observations that vitamin D depletion results in stimulation of enzyme activity. Results from these experiments indicate the wide species distribution of the renal enzyme required for the production of $1,25(OH)_2D_3$. Clearly, the production of this steroid hormone by the kidney has a universal distribution among vertebrates tested. A particularly intriguing question is the nature of evolutionary pressures resulting in localization of the production of this hormone in the kidney.

When measured under *in vitro* conditions in homogenates from whole tissue or purified subcellular components, the renal 25-OH-D_3-1-hydrolase system seems to have a higher capability or maximal velocity for turning out its product than does the liver enzyme, D_3-25-hydroxylase. These results contrast with those observed under *in vivo* conditions. Thus, the circulating concentrations of 25-OH-D_3 are much higher than those of $1,25(OH)_2D_3$. This suggests that the activity of the hepatic enzyme may be greater than that of the renal enzyme under *in vivo* conditions. However, the renal enzyme is probably subject to closer regulation than the hepatic enzyme responsible for conversion of D_3 to 25-OH-D_3.

At present, it would be premature to define the principal factors regulating the activation of vitamin D and the mechanisms for feedback control. From data obtained in several laboratories, it seems that increased conversion of 25-OH-D_3 to $1,25(OH)_2D_3$ occurs when dietary calcium is reduced following vitamin D deficiency, and with excess parathyroid hormone, while the opposite occurs with a high calcium diet, excessive calciferol intake and probably also in the absence of PTH. The interrelationships between 25-OH-D_3, $1,25(OH)_2D_3$ and PTH may prove to be highly complex: Thus, it has been suggested that $1,25$-$(OH)_2D_3$ may account for skeletal actions heretofore attributed to PTH,[46] and data have been reported suggesting that 25-OH-D_3 (or its active form, $1,25[OH]_2D_3$) may directly act on the parathyroid glands, possibly inhibiting the secretion of PTH.[91] Also, it has been reported in a preliminary communication that hypercalcemia and consequent PTH-suppression may reduce the plasma levels of 25-OH-D_3.[92]

As an analogy, it may be noted that a complex hormonal system regulating blood pressure and extracellular volume and involving serum potassium and sodium concentrations, renin, angiotensin and aldosterone has been characterized over

the past 15 years. During the next several years, it would not be surprising to see the unraveling of an equally complicated humoral system related to calcium homeostasis which includes serum (and perhaps intracellular) calcium and phosphate, vitamin D_3, 25-OH-D_3, 1,25$(OH)_2D_3$, parathyroid hormone and calcitonin.

Clinical Considerations of Vitamin D

Normal man

Before considering disease states that may be related to vitamin D and its metabolites, it is essential to have an understanding of the circulating concentrations of vitamin D metabolites in normal man, their rates of turnover, and the requirements of the target tissues for these various metabolites. It will then be possible to consider in more detail how various disease states may arise or affect the action of vitamin D or its metabolites.

Mawer, Stanbury and colleagues have carried out an extensive study of the turnover time of vitamin D_3 and 25-OH-D_3 in normal and vitamin D-deficient humans.[71,93] In addition, Belsey et al[74] and Haddad et al[75] have developed steroid displacement assays to measure the circulating concentrations of vitamin D and 25-OH-D.* It has been determined that the mean half-time (T½) for plasma disappearance of D_3 in man is 4.5 days, while the T½ for 25-OH-D_3 is 16 to 30 days. It has been estimated that the turnover time of 1,25$(OH)_2D_3$ is 1 to 10 days.[94] The findings of Haddad et al[75] indicate that circulating plasma concentrations of vitamin D and 25-OH-D are of the order of 15 to 30 nanograms (ng) per ml, and it can be calculated from the data compiled by Mawer et al[71] that the circulating concentrations of 1,25$(OH)_2D_3$ are much lower (10 to 100 picograms [pg] per ml) and Brumbaugh and associates have recently developed a competitive binding assay for 1,25$(OH)_2D_3$ and report normal levels of 80 pg per ml.[95,96] From these data, one can calculate the estimated daily production of 25-OH-D_3 and 1,25$(OH)_2D_3$ in man. It is likely that some 4,900 pmoles (equivalent to 75 U or 1.7 μg) of 25-OH-D_3 are produced each day while 300 to 1,500 pmoles (5 to 25 U or 0.14 to 0.68 μg per day) of 1,25$(OH)_2D_3$ must be produced daily by the kidney to maintain a steady state in normal man.

*Such steroid displacement assays do not differentiate between cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2) or their metabolites; therefore, the compounds are referred to simply as, vitamin D and 25-OH-D.

An interesting comparison can be made between the calculated need for 1,25$(OH)_2D_3$, as estimated from plasma turnover times and circulating concentrations, and the calculated capability of the renal enzyme to produce 1,25$(OH)_2D_3$, as measured under in vitro conditions. Since the circulating concentration of 25-OH-D_3 is known and its concentration is maintained at a level which would support a rate that is about 5 percent of the maximal velocity of the 1-hydroxylase, it can be extrapolated that a 70 kilogram man might produce 2,100 pmoles of 1,25$(OH)_2D_3$ per day on the basis of information obtained from renal enzymes from rachitic chicks. The calculations in the preceding paragraph suggest that as little as 250 pmoles per day of 1,25-$(OH)_2D_3$ may be normally produced by the human kidneys.

From such calculations and the results of measurements in other species it is likely that the relative concentration of the 25-OH-D_3-1-hydroxylase activity in the kidney of man is considerably below those present in other species. This could indicate that man may be unusually susceptible to environmental or disease-related factors which could damage the kidney or alter its enzymatic machinery. There may be little margin for error in the capability to produce this important steroid hormone, which is essential for normal homeostatic regulation of calcium. Indeed, there may be a delicate balance between the demand for this steroid hormone by the target tissues and the capability for its production by the kidney. With these considerations in mind, various disease states related to vitamin D will be reviewed.

Diseases that may be related in some fashion to vitamin D can be discussed from the standpoint of abnormal responsiveness to vitamin D (for example, hypersensitivity, antagonism or resistence to vitamin D) or from a systems-analysis standpoint (wherein a disease might be related to a problem involving either the production of the active form of vitamin D or the biological response of certain target organs). Any condition that impairs the ultimate production of 1,25-$(OH)_2D_3$ by the kidney or interferes with the factors involved in calcium homeostasis leading to abnormal feedback signals to the kidney could result in altered production of the hormone, 1,25-$(OH)_2D_3$. Thus, the kidney may be directly or indirectly implicated in a variety of diseases, some of which are noted in Chart 10.

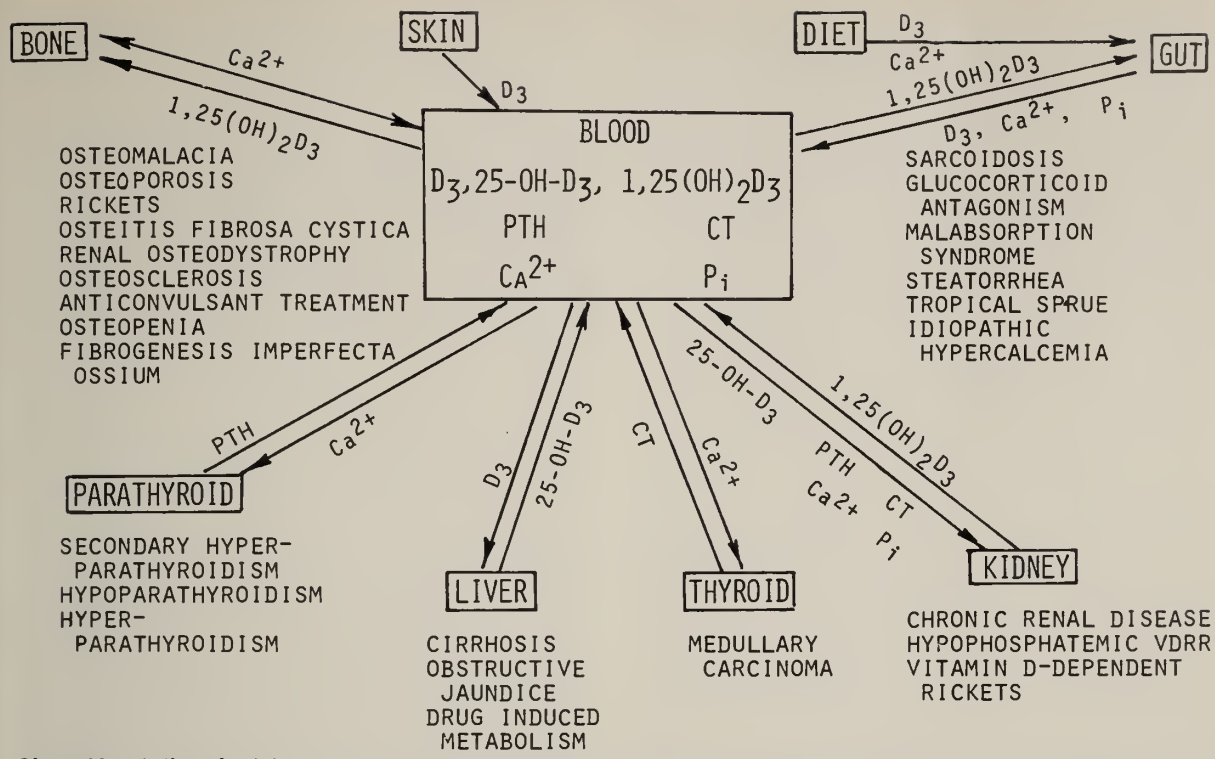

Chart 10.—A list of clinical disorders which may be related, directly or indirectly, to altered metabolism or action of vitamin D. Abbreviations include: CT, calcitonin; P_i, inorganic phosphate; others are described in the text.

Ultraviolet light and intestinal absorption

Under usual circumstances, adequate amounts of vitamin D are produced in the epidermis from 7-dehydrocholesterol through a photochemical reaction catalyzed by ultraviolet light. Essentially, few details are available to describe the biochemistry of this reaction. Following production of the prohormone, vitamin D, it presumably is absorbed into the circulation where it becomes specifically associated with a transport protein present in plasma. To date, no diseases are known to occur as a consequence of impaired absorption from the epidermis. However, clothing, air pollution and climatic conditions often reduce this process so that adequate vitamin D_3 is not produced in the skin. Under such circumstances, there is dependency upon a dietary source of vitamin D. Dietary vitamin D_2 or vitamin D_3 is absorbed principally in the jejunum[97,98] into the lymphatic system. This is facilitated by bile salts and the formation of chylomicrons.[99]

In man, vitamin D_2 and D_3 are equally effective, in contrast to birds and new-world primates where vitamin D_2 is less effective than vitamin D_3. The recommended daily intake of 400 IU of vitamin D is generally adequate in adults, growing children and pregnant or lactating women. It has been documented that clinically apparent deficiencies of vitamin D can develop in adults ingesting less than 70 IU per day.[100] With supplementation of milk and bread with ergocalciferol (D_2), as is required in the United States, vitamin D-deficiency is rare. However, it is being detected in Asian immigrants to Western Europe[101,102] and also in patients whose diets are low in fat and restricted in certain proteins.[103,104] In general, the best natural sources for vitamin D are eggs, butter, cream, liver and fish. Non-irradiated cows milk, human milk and other meat sources are relatively low in vitamin D content.[105]

The most common causes of vitamin D-deficiency in Western Europe and the United States are the various intestinal disorders leading to malabsorption of vitamin D. Thus, there is clear evidence for decreased absorption of vitamin D in steatorrhea and the malabsorption syndromes, and also in biliary cirrhosis.[99,106] There is little direct evidence showing the feasibility or effectiveness of overcoming these problems by a simple increase in the dietary intake of calciferol.

Liver disease and altered hepatic function

After the association of calciferol with its appropriate serum binding protein, an alpha-2

globulin with a molecular weight of 50,000 to 60,000,[107,108] it is transported to the liver. Here it undergoes hydroxylation at carbon-25 of its side chain. There is a wide range of hepatic malfunction which potentially may interfere with this key metabolic transformation. These disorders include cirrhosis, either Laennec's or post-necrotic, or hepatitis. With biliary cirrhosis, there may be altered absorption of calciferol, as well as defective conversion to 25-OH-D_3. Although clinically obvious osteomalacia is not known to be frequent in patients with hepatic disease, extensive studies evaluating skeletal histology or intestinal absorption of calcium are not available. It has been shown that there is delayed plasma disappearance of radioactive vitamin D in patients with hepatocellular dysfunction.[109] Moreover, reduced plasma levels of 25-OH-D have been found in patients with biliary cirrhosis in association with poor absorption of radiocalcium (Chart 9). Moreover, there is prompt improvement to treatment with 25-OH-D_3, while D_3 itself is nearly without effect.[73]

Recently, evidence has accumulated that prolonged use of anti-convulsant drugs, such as phenobarbital or diphenylhydantoin (Dilantin®), may lead to an impaired response to vitamin D.[110-113] Therefore, hypocalcemia may occur in 20 to 30 percent of epileptics receiving anticonvulsants, and biopsy studies of bone show florid osteomalacia.[110] These patients generally respond to treatment with supplemental vitamin D.[110] Reduced plasma levels of 25-OH-D have been observed in patients receiving anticonvulsant drugs.[72] From studies with experimental animals, the suggestion has been made that anticonvulsant-induced vitamin D deficiency results from stimulation of hepatic microsomal P-450 enzymatic activity by the drugs.[114,115] This results in accelerated turnover of vitamin D_3 and 25-OH-D_3 to more polar inactive compounds and decreases the availability of 25-OH-D_3, which may lead to a lowered production of 1,25-$(OH)_2D_3$ by the kidney. Preliminary data obtained in our laboratory suggest that a phenobarbital-induced vitamin D-deficient state can be overcome by administration of small quantities of 1,25$(OH)_2D_3$ in experimental animals.[114] In view of the widespread use of anticonvulsants, tranquilizers, various sedatives and oral antidiabetic compounds (all of which are capable of inducing microsomal hydroxylase activities),[116] it is apparent that there may be potential for the development of a number of drug-induced vitamin D-deficient states. This is particularly the case with continued long-term use of such drugs.

Renal disease

Chronic renal insufficiency is an important pathophysiologic state believed to adversely affect the metabolism of vitamin D.[117-121] Although an association between renal disease, skeletal abnormalities and hyperplasia of the parathyroid glands has been known for several decades, the incidence and clinical significance of abnormalities of divalent ion metabolism, soft tissue calcification and osseous pathology has been more clearly recognized with the advent of treatment with hemodialysis, renal transplantation and improved conservative therapy. The term "renal osteodystrophy" has been used to denote the skeletal abnormalities occurring in patients with chronic renal failure; these include retardation of growth, osteomalacia, osteitis fibrosa, osteoporosis and osteosclerosis. The derangements in divalent ion metabolism in patients with reduced renal function include hypocalcemia, hyperphosphatemia, abnormal vitamin D metabolism, defective intestinal absorption of calcium, hyperplasia of the parathyroid glands, soft tissue calcification and bone disease.

During the past ten years, there has developed renewed interest in renal osteodystrophy and the disorders of divalent ion metabolism which accompany chronic renal failure. In large measure, this interest has arisen due to the realization that there is a high incidence of clinically apparent bone disease with prolonged treatment with hemodialysis.[122] Hyperphosphatemia, hypocalcemia and secondary hyperparathyroidism have been considered by some to play the foremost part in the pathogenesis of deranged divalent ion metabolism in uremia. However, there are clinical similarities between nutritional vitamin D-deficiency and certain observations in chronic renal failure.[48,123] Thus, impaired growth and deformities of long bones have been described in children with chronic renal failure.[124]

Moreover, such patients fail to respond to treatment with the quantities of calciferol that are effective in children with nutritional rickets.[48,120] Also, histologic findings of increased uncalcified osteoid have been clearly documented. Garner and Ball found that the mass of mineralized bone was approximately normal while the uncalcified osteoid was increased above that normally expected.[125] More recent studies have verified the

occurrence of osteomalacia in a sizable fraction of uremic patients.[126-128]

In patients with renal failure, diminished intestinal absorption of calcium was suggested by results of metabolic balance studies which indicated that fecal calcium was equal to or exceeded the quantity ingested.[48,120,123] With use of radioisotopic methods, the intestinal absorption of calcium was found by numerous investigators to be reduced in uremic patients.[129-131] Further, it has been shown that such impaired intestinal absorption of calcium may be minimized or overcome under situations of very large calcium intake.[132,133] Despite this apparent inconsistency, most studies show impaired absorption of calcium in uremic patients, particularly when they are tested while receiving their usual calcium intake.[131]

The concept that uremia may impair the response to vitamin D was pioneered by Liu and Chu,[120] who found no improvement of osteomalacia or calcium absorption in uremic patients treated with usual oral doses of vitamin D. However, the intestinal malabsorption of calcium could be overcome by the administration of vitamin D in doses of 100,000 to 300,000 IU per day.[48,123] With this increased absorption of calcium, the rickets or osteomalacia is generally healed. Such observations led to the speculation that the intestinal absorptive mechanism for calcium was unresponsive unless the total vitamin D "activity" in the plasma was increased to very high levels.[134] The subsequent identification of the kidney as the organ involved in the final conversion of vitamin D to its active form has provided a reasonable explanation for these earlier observations.

Experiments have been carried out to explore the cause or pathogenesis of abnormal calciferol action in uremia: the intestinal absorption of calciferol is normal in uremic patients.[135] Avioli and co-workers[109] suggested that the turnover of D_3 proceeds unusually rapidly in uremic subjects with increased production of nonactive metabolites. Also, low plasma levels of 25-OH-D_3 were found in uremic rats, in comparison to the levels found in pair-fed, sham-operated controls.[136] On the other hand, Lumb et al[137] and Mawer and co-workers[71] compared the metabolism of ^{3}H- or ^{14}C vitamin D_3 in uremic patients and normal subjects and concluded that the production and turnover of 25-OH-D_3 were normal. They considered that the results of Avioli and co-workers occurred because of a lower dietary intake of nonradioactive vitamin D in the uremic patients. Also, normal levels of 25-OH-D have been observed in serum of uremic patients[73,138,139] Moreover, there has been little success in the treatment of renal osteodystrophy with large doses of 25-OH-D_3.[140] The weight of available evidence, therefore, favors the view that defective production of 25-OH-D_3 is not primarily responsible for impaired calcium absorption and osteomalacia in uremic man.

Since the kidney produces $1,25(OH)_2D_3$ from its precursor, it has been attractive to speculate that impaired renal production of $1,25(OH)_2D_3$ accounts for the impaired calcium absorption and osteomalacia in uremia. Considerable data are consistent with this premise. Thus, investigators in several laboratories have shown that nephrectomized rats fail to produce $1,25(OH)_2D_3$.[10-12] Mawer and co-workers[141] and Schaefer et al[142] found measurable displacement or loss of tritium after giving 1,2-^{3}H-4-^{14}C-D_3 to patients with normal renal function and dietary deficiency of calciferol but they found no tritium loss in anephric or uremic individuals; these data provide indirect evidence for the failure of uremic patients to produce $1,25(OH)_2D_3$.* Also, Piel, Roof and Avioli[143] found a metabolite of D_3, identical to $1,25(OH)_2D_3$, in plasma of uremic children following successful renal transplantation while none could be identified prior to the procedure (Chart 11). In addition, small quantities of $1,25(OH)_2$-D_3, but not its precursors, have been shown capable of mobilizing bone mineral and improving calcium transport in acutely uremic rats.[144] Also, $1,25(OH)_2D_3$ can elevate ^{47}Ca absorption to normal in patients with chronic renal disease (Chart 12),[145] and Hartenbower and associates[146] found decreased intestinal transport of calcium in association with reduced intestinal localization of $1,25(OH)_2D_3$ in chicks with impaired renal function.

Certain observations are inconsistent with the universal existence of decreased production of $1,25(OH)_2D_3$ in chronic renal disease. Thus, lesions of osteomalacia are by no means uniform and may occur in only a small fraction of cases; even in anephric subjects, bone biopsy studies may not reveal evidence of vitamin D deficiency.[147] In the absence of treatment with massive amounts of vitamin D steroids, it remains unclear why manifestations of vitamin D-defi-

*When hydroxylation occurs, there is displacement of the hydrogen from the specific carbon-position; hence, the hydrogen at the 1-α position is "lost" during the 1-hydroxylation.

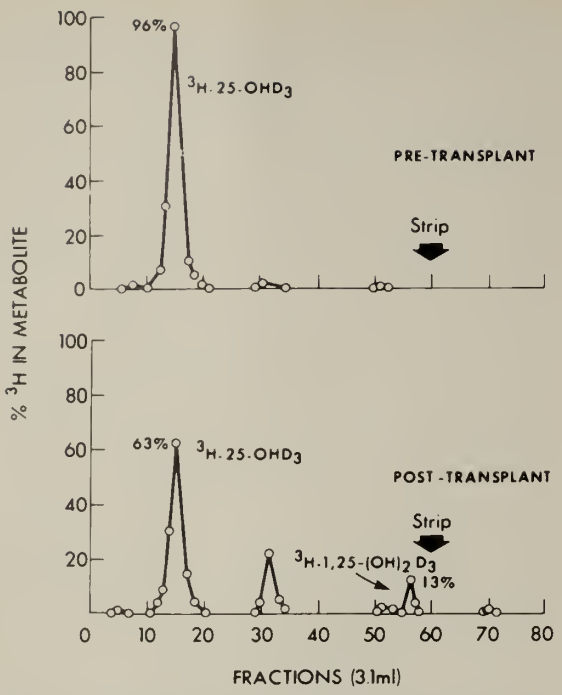

Chart 11.—Pattern of lipid soluble radioactivity (^{3}H) found in plasma eluted from a Sephadex LH 20 column. Plasma samples were obtained 24 hours after injections of ^{3}H-25-OH-D$_3$, both before and after successful renal transplantation (from Piel, et al,[143] with permission).

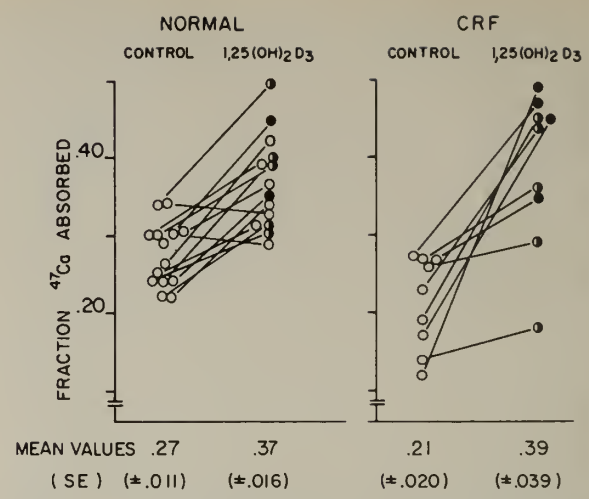

Chart 12.—The absolute fraction of ^{47}Ca absorbed in normal subjects and patients with chronic renal failure (CRF) before and after treatment with 1,25(OH)$_2$D$_3$. Lines connect results in the same subject. Quantities of 1,25 (OH)$_2$D$_3$ given include 2.7μg per day (●), 0.68μg per day (◑), and 0.14μg per day (O). Reprinted with permission.[154]

ciency fail to develop in such individuals. It is also uncertain why treatment with massive quantities of vitamin D$_2$ or D$_3$, per se, are capable of healing the osteomalacia in patients with advanced renal disease. Possible explanations include the capability of very large quantities of vitamin D to effect a certain degree of binding to receptors for 1,25(OH)$_2$D$_3$ and thus evoke a biologic action. It is well known that certain adrenal steroids, given in massive quantities, can produce the biological response of certain sex steroids, providing an analogy for this explanation. It is also theoretically possible that an organ other than the kidney may be capable of producing very small amounts of 1,25(OH)$_2$D$_3$.

Over 30 years ago, Liu and Chu[120] demonstrated that dihydrotachysterol (DHT) was effective in patients with renal disease while vitamin D$_3$ was not (Chart 13). These observations have been confirmed and extended by Kaye and coworkers.[148] With the chemical identification of 1,25(OH)$_2$D$_3$ and realization that its unique characteristic is the presence of a hydroxyl and the "one" carbon, it was apparent that DHT has certain structural similarities to the 1,25(OH)$_2$D$_3$ (Chart 13). Thus, the "A" ring of DHT is rotated in relationship to vitamin D, resulting in the hydroxyl at carbon-3 occupying a "pseudo-carbon number-1" position; in other words the hydroxyl at carbon number 3 of DHT has a similar stereo-chemical position as the one-hydroxyl of 1,25(OH)$_2$D$_3$ (Chart 14). It was not long before the ingenuity of the chemist produced 5,6-trans-vitamin D$_3$; 25(OH)5,6-trans-D$_3$; and 1 α (OH)-D$_3$, each of which may be considered as chemical analogs of the natural steroid, 1,25(OH)$_2$-D$_3$.[149-151] The 5,6-trans isomers can be produced readily with simple chemical conditions that mediate the cis-trans isomerization of the 5,6 double bond. Chemical synthesis of 1α(OH)D$_3$ represents a more remarkable feat, inasmuch as it is more difficult to introduce a hydroxyl group at carbon number 1 by chemical means.

Preliminary studies with these analogs suggest that their "pseudo-1" character allows them to produce biological actions obtained with D$_3$ or 1,25(OH)$_2$D$_3$.[149-151] Thus, 1α(OH)D$_3$; 5,6-trans-D$_3$; and 25(OH) 5,6-trans-D$_3$ each produced stimulation of intestinal calcium transport and bone calcium mobilization in anephric rats. Results from such studies suggest that a number of steroids, both natural and synthetic analogs, may eventually become available to permit the most beneficial manipulation of calcium metabolism by the clinician. Widespread clinical experience with the use of vitamin D and its analogs is limited to vitamin D$_2$ and D$_3$, and DHT,

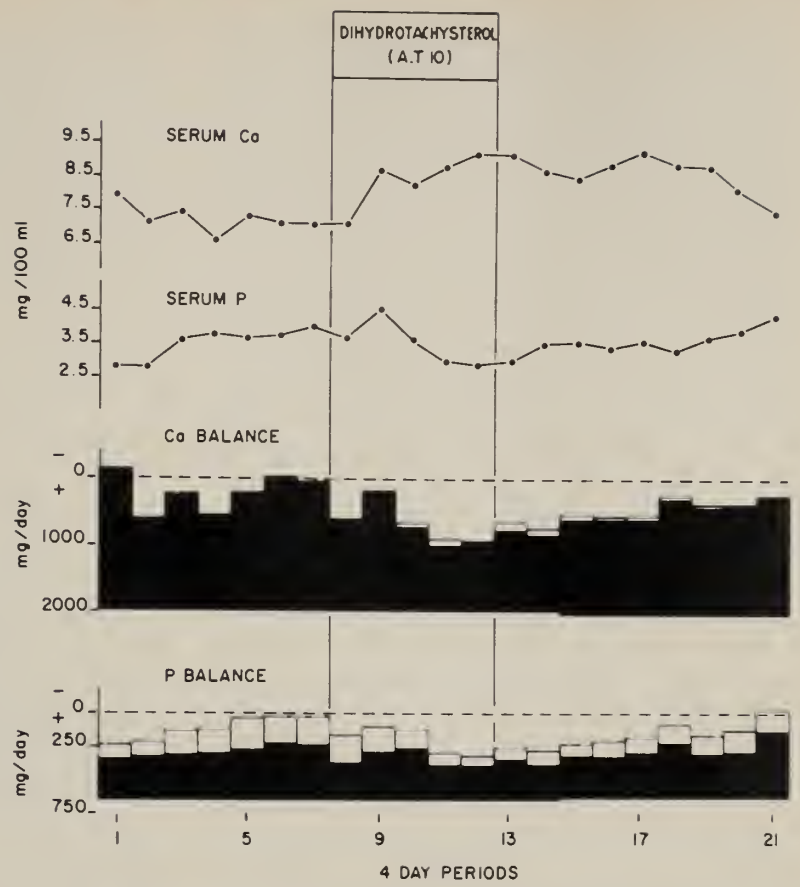

Chart 13.—Changes in serum calcium and phosphorus levels and metabolic balance for calcium and phosphorus in a patient with advanced renal failure who was treated with dihydrotachysterol. Data are adapted from Liu and Chu.[120] Fecal losses are designated by solid columns with urinary excretion represented by open columns.

although results in small numbers of patients are available with $1,25(OH)_2D_3$[145,152-156] and 1α-$(OH)D_3$.[157]

Massive quantities of D_2 can heal osteomalacia in patients with advanced renal failure.[48,123] A relatively wide margin of safety may exist because very little or none of the steroid is converted to the active form. However, when toxicity does occur, the effect may be quite prolonged. From the work of Liu and Chu[120] and Kaye and co-workers,[148] DHT may be the best commercially available agent for treatment of uremic patients who require such therapy. The promising actions of $1,25(OH)_2D_3$ in reversing skeletal lesions of secondary hyperparathyroidism and reducing the plasma levels of parathyroid hormone raise the possibility that this steroid may have a direct inhibitory effect on the parathyroid gland;[158] certain data obtained in rachitic puppies are consistent with such a possible action.[91]

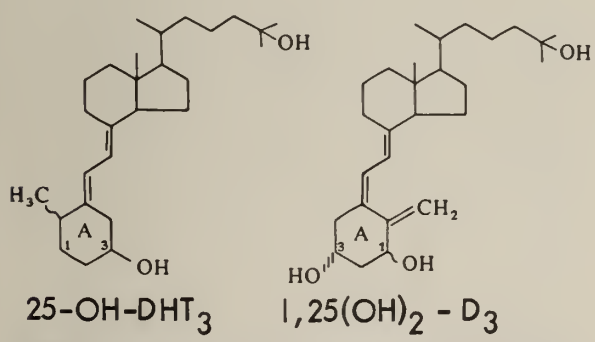

Chart 14.—Comparison of the structures of 25-hydroxydihydrotachysterol and 1,25-dihydrocholecalciferol. The former represents the form of dihydrotachysterol (DHT) after its hydroxylation at the 25-position by the liver.

Hypophosphatemic rickets (vitamin D-resistant rickets)

An example of a disease or group of diseases which may be related to abnormal vitamin D-action is "vitamin D-resistant" rickets (VDRR). This term has been applied to a variety of clinical conditions detected during childhood because of retardation of growth and skeletal deformities which resemble those of rickets and are unresponsive to normal or even massive quantities of vitamin D. X-linked "hypophosphatemic rickets," an inherited disease transmitted through a single dominant gene on the X-chromosome, is the most clearly defined single disorder.[159] It is manifested

by rickets or osteomalacia in severe cases and only hypophosphatemia in its milder form. The hypophosphatemia is believed to be due principally to reduced renal tubular reabsorption of phosphate. There is disagreement as to whether decreased renal tubular reabsorption of phosphate is due to secondary overactivity of the parathyroid glands as a result of hypocalcemia or arises directly from an impairment in phosphate transport by the renal tubule. It has been suggested that VDRR may result from altered metabolism of vitamin D;[160] however, there has been no experimental evidence to support this suggestion. Thus, the circulating levels of 25-OH-D were no different in normal and VDRR subjects.[161] Moreover, treatment of patients with VDRR with $1,25(OH)_2$-D_3 in amounts up to 2.7 μg per day failed to correct the renal phosphate wasting, although intestinal absorption of calcium was enhanced.[153] Thus, current evidence suggests that this condition is not due to altered metabolism of D_3 to $1,25(OH)_2D_3$ nor to impaired response of the intestine to the latter. It seems more likely that VDRR represents a specific defect in tubular transport of phosphate. Another disorder, which is phenotypically similar, has also been described with an autosomal dominant pattern of transmission.[162] Current views concerning the pathogenesis and management of these disorders are described in detail elsewhere.[163-165]

Vitamin D-dependent rickets (pseudo-vitamin D-deficiency rickets)

Vitamin D-dependent rickets, first recognized about ten years ago,[166] is much less common than VDRR. This disorder differs from primary hypophosphatemic rickets (vitamin D-resistant rickets) in that hypocalcemia is regularly present and from nutritional rickets (vitamin D-deficiency) in that pharmacologic doses of vitamin D are necessary to correct the osseous disease. Indeed, when afflicted children are treated with vitamin D_2, 10,000 to 50,000 IU per day, there is correction of the biochemical abnormalities, and "catch-up" growth usually occurs. This condition appears to have an autosomal recessive pattern of inheritance.[166,167] Data presently available suggest that this disease may arise due to altered metabolism of vitamin D in that Fraser et al reported a patient to be highly sensitive to very small quantities of $1,25(OH)_2D_3$.[168] Comparable observations in another case have been presented by Balsan and co-workers.[169] In contrast, studies by Rosen and Finberg[170] failed to show a significant response with much larger quantities of 25-OH-D_3. It is likely that patients with vitamin D-dependent rickets are deficient in the 1-hydroxylase which mediates the formation of $1,25(OH)_2$-D_3 from 25-OH-D_3. Thus, this disease appears to be the first recognized disorder due to a congenital abnormality affecting the metabolism of vitamin D.

Fibrogenesis imperfecta ossium

Fibrogenesis imperfecta ossium is a rare disorder, characterized by the appearance in adults of osteomalacia with marked bone pain and tenderness.[171] There is normal intestinal absorption of calcium, and, likewise, serum levels of calcium and phosphorus are normal. Skeletal biopsy studies show histologic evidence of osteomalacia with defective collagen formation.[172] In one case the administration of vitamin D was followed by an initial response, but resistance later developed. Dihydrotachysterol was effective throughout the period of observation.[173] Whether this disease is due to defective metabolism or action of calciferol remains unknown. The response to DHT may represent a pharmacologic action of this steroid that does not occur with vitamin D_2 or D_3 because of feedback control of their metabolism. One might anticipate that $1,25$-$(OH)_2D_3$ might also be effective, but doses larger than "physiologic" might be required. Obviously, more information is needed for clarification of the cause and proper management of this rare disorder.

Hypoparathyroidism

Since parathyroid hormone (PTH) may be a trophic factor stimulating the production of $1,25$-$(OH)_2D_3$ from its precursor, 25-OH-D_3,[80,82] and since therapy with pharmacologic quantities of vitamin D_2 represents the usual form of management of hypoparathyroidism, a consideration of vitamin D metabolism in this condition seems appropriate. Certain clinical observations support the proposal that alterations in parathyroid gland activity may affect vitamin D metabolism. Thus, marked resistance to the action of massive doses of vitamin D_2 or D_3 may occur in patients with hypoparathyroidism,[174,175] and the response to a given quantity may be unpredictable. Treatment with $1,25(OH)_2D_3$ (2.7 μg per day) had a pronounced effect on serum and urinary calcium when it was used in conjunction with 5 mg per

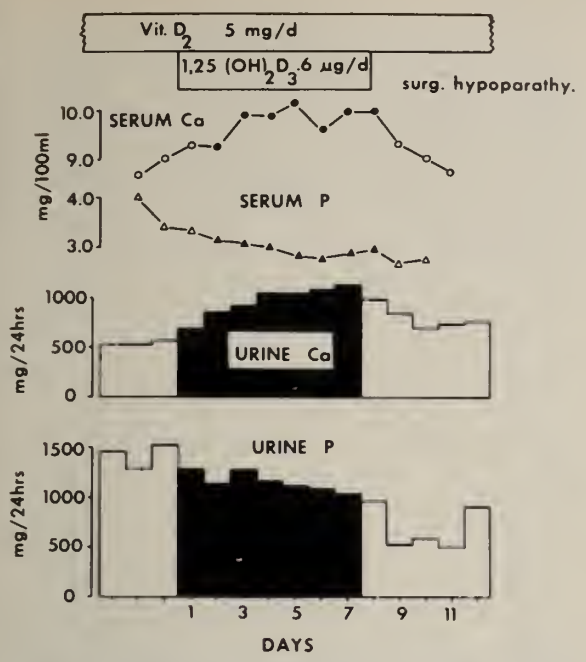

Chart 15—Effects of 1,25(OH)$_2$D$_3$ on calcium balance in a patient with surgical hypoparathyroidism. The patient received ergocalciferol (vitamin D$_2$), 5mg or 200,000 IU per day, plus his usual supplemental dietary calcium (2 g per day) throughout the study. Reprinted from Coburn, et al, with permission.[176]

day of vitamin D$_2$ (Chart 15).[176] Therapy with 25-OH-D$_3$, in daily doses of 15 to 125 µg, had a prompt action in most, but not all, patients with hypoparathyroidism.[177-178] If parathyroid hormone represents an important factor regulating the production of 1,25(OH)$_2$D$_3$ from 25-OH-D$_3$,[80,82,83] this might account for the poor response to the precursor, vitamin D. The suggestion that PTH may exert its effort on vitamin D metabolism by altering serum or intracellular phosphate levels[85] may explain resistance in such patients since hyperphosphatemia is commonly present in those with hypoparathyroidism. The margin between an effective and a toxic dose of vitamin D$_2$ may be narrow and unpredictable, and toxicity may persist for some time after the drug has been withdrawn. Thus, 1,25(OH)$_2$D$_3$ or its potent analogs may eventually be valuable therapeutic agents, with more rapid and predictable effects and a shorter duration of action.

Hyperparathyroidism

Clinical evidence for abnormal action of vitamin D in primary hyperparathyroidism has been described by Woodhouse, Doyle and Joplin;[179] they described radiologic improvement in the lesions of osteitis fibrosa in patients with hyperparathyroidism following treatment with vitamin D$_2$, 1.25 mg per day. Pronounced hypercalcemia did not develop, and alkaline phosphatase values fell to normal during treatment. In addition, Jowsey[180] and Avioli[181] have observed a high frequency of histologic features of osteomalacia in bone specimens taken for biopsy from patients with primary hyperparathyroidism. Such findings might be due to either reduced formation or more rapid degradation of 1,25(OH)$_2$D$_3$. On the other hand, the intestinal absorption of calcium is often increased in patients with hyperparathyroidism,[182,183] while intestinal transport of calcium is reduced in experimental animals following parathyroidectomy.[184] Despite such observations, attempts to demonstrate a direct and immediate action of PTH on intestinal calcium transport have failed.[184] It is possible that hyperabsorption of calcium is due to increased production of 1,25-(OH)$_2$D$_3$ in patients with hyperparathyroidism or is a consequence of increased sensitivity of the intestine to the 1,25(OH)$_2$D$_3$ present. The postulate that there is increased formation of 1,25-(OH)$_2$D$_3$ is consistent with experimental work from several laboratories.[80,82,83]

Sarcoidosis

Hypercalcemia and hypercalciuria not infrequently occur in patients with sarcoidosis, and these abnormalities are usually associated with a decrease in fecal calcium.[185] The hypercalcemia may appear after patients with sarcoidosis have received relatively small doses of vitamin D.[186,187] Exacerbation of hypercalcemia in sarcoidosis following greater seasonal exposure to sunlight[188] and the remission of hypercalcemia after elimination of exposure to ultraviolet light[189] provide evidence for the theory that there is an increased "sensitivity" to vitamin D in this disorder. The cause for such increased sensitivity remains obscure: plasma levels of total vitamin D (antirachitic activity) have been found to be normal,[186] as are plasma levels of 25-OH-D (Chart 9).[73] The plasma turnover of radioactive vitamin D$_3$ has been reported to proceed abnormally rapidly in these patients.[190] However, normal conversion of 25-OH-D to 1,25(OH)$_2$D$_3$ has been reported.[191]

It is well known that the hypercalcemia of sarcoidosis responds readily to treatment with cortisone or other glucocorticoids.[185,186] Glucocorticoids are known to inhibit the action of calciferol steroids both in enhancing intestinal trans-

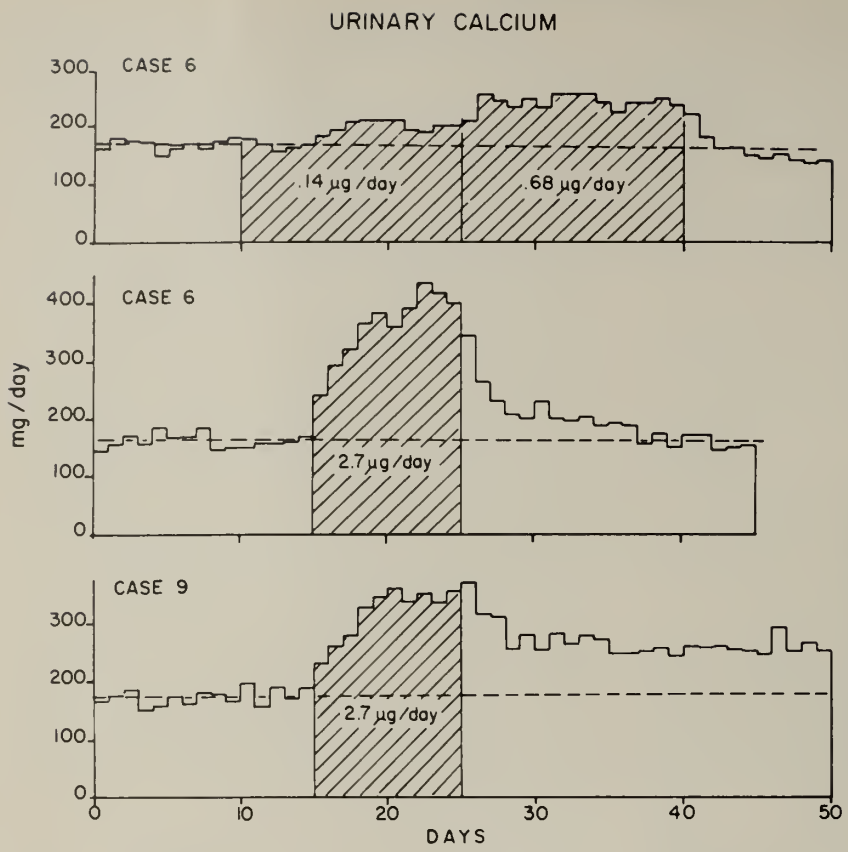

Chart 16.—Changes in daily urinary excretion of calcium in normal subjects receiving a constant dietary intake of calcium and treated with $1,25(OH)_2D_3$. The cross-hatched areas indicate the periods of treatment. Reprinted from Brickman et al, with permission.[156]

port of calcium[192-194] and in stimulating bone resorption.[195] Therefore, it is attractive to propose that steroids ameliorate the hypercalcemia of sarcoidosis by inhibiting the action of vitamin D. However, the mechanism whereby glucocorticoids inhibit vitamin D-stimulated intestinal transport of calcium remains uncertain. The bulk of reported data indicates that conversions of D_3 to 25-OH-D_3 and of 25-OH-D_3 to $1,25(OH)_2$-D_3 proceed normally during treatment with cortisone;[196] also, there is normal localization of $1,25$-$(OH)_2D_3$ in the intestinal cell nuclei. It has been suggested that the defect in calcium transport occurs due to an abnormality in the transport mechanism rather than due to altered vitamin D metabolism.[196] In other words, cortisol may cause the end-organs to become resistant to the action of calciferol or its metabolites.

Idiopathic hypercalciuria

The major clinical significance of hypercalciuria is its relation to the genesis of renal stones; it has been reported that 20 to 33 percent of patients with renal stones may have hypercalciuria.[197,198] A large number of these patients have been characterized as having "idiopathic hypercalciuria"[199-202] (that is, hypercalciuria without a known cause), thereby excluding hyperparathyroidism, diseases causing bone resorption, excessive dietary intake of calcium or vitamin D, and various renal tubular defects. More often these patients are males with normal levels of serum calcium, normal or slightly reduced serum phosphorus concentrations, and renal stones which usually consist of calcium oxalate. Intestinal absorption of calcium is often increased in these patients,[203,204] and this abnormality may be the pathogenetic mechanism underlying the hypercalciuria.[205,206] With rigid restriction of calcium intake, its renal excretion does fall;[205,206] also, urinary calcium increases inordinately when dietary calcium intake is augmented.[207]

Another possible explanation for the hypercalciuria is defective renal tubular reabsorption of calcium. In support of this, Edwards and Hodgkinson found increased renal clearance of calcium while its filtered load was below normal.[199] Also, Coe, Canterbury and Reiss[208] reported increased plasma levels of PTH in patients with this disorder. They proposed that primary losses of urinary calcium lead to small decrements in plasma calcium, which stimulates re-

lease of PTH, with the increase in calcium absorption and low levels of serum phosphorus occurring secondary to the action of PTH. Observations that urinary calcium returns to normal following restriction of dietary calcium intake[205,206] and the finding of normal urinary excretion of calcium in a transplant recipient who had received a kidney from a donor with idiopathic hypercalciuria[209] are inconsistent with renal tubular defect of calcium reabsorption being the primary factor in the genesis of the hypercalciuria. From calcium balance and kinetic studies with radiocalcium, Liberman and coworkers,[203] reported increased rates of calcium turnover in bone and suggested a fundamental disturbance of calcium metabolism leading to the high calcium turnover.

It is likely that "idiopathic hypercalciuria" may represent more than one disorder. Urinary calcium can abruptly increase in normal humans when the efficiency of its absorption is increased by either dietary manipulation[210] or following the administration of $1,25(OH)_2D_3$[156] creating a situation resembling that described in idiopathic hypercalciuria (Chart 16). Therefore, it is possible that certain patients with this disorder could have either increased renal production of $1,25-(OH)_2D_3$ or enhanced intestinal sensitivity to the steroid.

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Refer to: Mendoza SA, Keller M: Inappropriate secretion of antidiuretic hormone—Pediatric Grand Rounds, University of California, San Diego, and University Hospital of San Diego County (Specialty Conferences). West J Med 121:45-49, Jul 1974

Specialty Conference

Participants

STANLEY A. MENDOZA, MD
MARGARET KELLER, MD

Taken from the weekly Pediatric Grand Rounds held at the University Hospital of San Diego County, University of California, San Diego, School of Medicine

Inappropriate Secretion of Antidiuretic Hormone

DR. KELLER:* A 16-month-old white boy was admitted to hospital following one day of fever and obtundation. He was well until four days before admission when a nasal discharge and cough developed. On the day of admission a temperature of 104°F had been noted. He had become obtunded, crying only when touched. Consequently, he was seen at the United States Naval Hospital, San Diego, where a lumbar puncture was done. The spinal fluid contained 2,700 leukocytes per cu mm with 94 percent polymorphonuclear leukocytes and many Gram-negative coccobacilli.

The patient was transferred to University Hospital. On admission a temperature of 101°F was recorded, with a pulse rate of 140 and a respiratory rate of 44 per minute. Blood pressure was normal. The pertinent positive physical findings were pronounced nuchal rigidity; a dull, thickened right tympanic membrane; and a slight amount of clear rhinorrhea. The blood and cerebrospinal fluid cultures grew Hemophilus influenza.

Ampicillin was given parenterally at a dosage of 300 mg per kg of body weight every 24 hours. Fluids were given at a rate half that of his calculated maintenance requirements. The fever cleared on the second hospital day. On day one, oliguria developed. Tests of urine showed a specific gravity of 1.042 and an osmolality of 882 milliosmols (mOsm) per kg of H_2O. A test of serum osmolality done at the same time gave results of 270 mOsm per kg of H_2O. A diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) was made. The laboratory data are summarized in Table 1.

On day two, ethyl alcohol was given by mouth and the urine specific gravity fell to about 1.010. Fluid administration was decreased to a rate one-third that of the calculated maintenance fluid requirements and additional fluid was given to replace the volume of urine excreted. On day three, ethyl alcohol was again given but there was no increase in the volume of urine output. On day four, the patient began to show clinical improvement in his level of consciousness. Strict fluid restriction was continued and by day five urine osmolality and serum osmolality had become appropriate. The remainder of his hospital course was unremarkable.

DR. MENDOZA:† The syndrome of inappropriate antidiuretic hormone secretion is one which many consider a rare and esoteric problem. One of the points that I want to make is that, at least in a mild form, SIADH is a common problem in pediatrics. It occurs most frequently after meningitis and after surgical operation. In general, the syndrome is so mild that it causes no symptoms because patients at risk are routinely given a

*Margaret Keller, MD, Intern in Pediatrics.

Reprint requests to: S. A. Mendoza, MD, Chief, Division of Pediatric Nephrology, Department of Pediatrics, University of California, San Diego, School of Medicine, P.O. Box 109, La Jolla, CA 92037.

†Stanley A. Mendoza, MD, Associate Professor of Pediatrics.

TABLE 1.—*Laboratory Data of the Patient Presented*

Day	Wt. kg	Fluid intake ml	Fluid output ml	U_{osm} mOsm/kg	P_{osm} H_2O	Serum[Na] mEq/L
1 ...	8.9	380	70	..	..	..
2 ...	8.9	435	115	882	270	136
3 ...	9.0	335	100	421	269	136
4 ...	9.1	405	280	535	..	132
5 ...	8.9	630	513	58-257	257	..

U_{osm} and P_{osm} refer to the osmolality of the urine and serum, respectively.

TABLE 2.—*Criteria for the Diagnosis of SIADH*

1. No dehydration
2. Hyponatremia and hypoosmolality
3. Normal renal function
4. Normal adrenal function
5. Urine inappropriately concentrated
6. Urinary sodium excretion present

lower fluid intake than the usual maintenance fluids.

The best place to begin in discussing SIADH is with a short discussion of the renal concentrating mechanism, with an emphasis on what antidiuretic hormone (ADH) does and on the appropriate stimuli for ADH secretion. After the appropriate conditions for ADH secretion are clear, we can go on to discuss inappropriate ADH secretion.

In the nephron, filtration occurs at the glomerulus. Throughout the proximal tubule, there is active reabsorption of sodium. The proximal tubule is highly permeable to water so that when sodium is actively reabsorbed, water is passively reabsorbed. Therefore, the osmolality of proximal tubular fluid remains the same as that of plasma (approximately 300 mOsm per kg of H_2O). The tubular fluid then enters the loop of Henle, which passes through the medulla.

The medullary interstitium is hypertonic and has a high concentration of both sodium and urea. As the tubular fluid moves along the descending limb of the loop of Henle, water diffuses from the lumen along its osmotic gradient and at the same time sodium and urea diffuse into the lumen. The relative magnitude of solute influx and water efflux is controversial. Both mechanisms result in a tubular fluid that is increasingly hypertonic as it moves along the descending limb of the loop of Henle. The osmolality reaches about 1,200 mOsm per kg of H_2O at the so-called "hairpin turn."

The ascending limb of the loop of Henle is impermeable to water. Essentially no water leaves or enters the lumen, but the tubular fluid becomes diluted, because sodium chloride both diffuses and is actively transported from the ascending limb. By the time the tubular fluid reaches the early distal tubule, its osmolality is about 100 mOsm per kg of H_2O. The changes in tubular fluid osmolality which occurs before this point in the nephron occur whether the animal is in maximum water diuresis or in maximum antidiuresis. In other words, the tubular fluid is dilute in the early distal tubule even in the presence of a maximal concentration of circulating ADH.

The major effect of ADH is to increase the permeability to water of the distal tubule and collecting duct. As a result of the increased permeability, water diffuses from the tubular lumen and the osmolality of the tubular fluid becomes equal to that of the surrounding interstitial fluid. In the distal tubule and cortical collecting duct the tubular fluid becomes isotonic to plasma in the presence of ADH. As the tubular fluid passes through the medullary collecting duct, it becomes increasingly hypertonic as it is exposed to the increasingly hypertonic medullary interstitium. In maximum antidiuresis, the final urine osmolality is 1,200 to 1,400 mOsm per kg of H_2O. Thus, in the presence of ADH, the kidney reabsorbs water in the distal tubule and collecting duct. This water is reabsorbed largely in the absence of solute (free water is reabsorbed).

The two physiologic stimuli for the secretion of ADH are: (1) an increase in the osmolality of the extracellular fluid; and (2) a decrease in the extracellular fluid volume. These stimuli are logical teleologically. ADH causes increased water reabsorption, and the two situations in which water reabsorption is appropriate are hyperosmolality and volume depletion.

Table 2 gives criteria for the diagnosis of SIADH. First, there must be no dehydration. If the patient's extracellular fluid volume is diminished, he has ADH secretion but it is physiologically appropriate. Second, there must be a low serum sodium concentration and, therefore, a low serum osmolality. If the serum sodium concentration and the serum osmolality are high, ADH secretion is physiologically appropriate. Third, there must be normal function of the kidneys and of the adrenal glands. Dysfunction of either organ can cause abnormal salt and water metabolism and hypoosmolality independent of ADH. Fourth, the osmolality of the urine must be higher than is appropriate for the patient's condition. The urine does not have to be more concentrated than plasma in order to be inappropriate, since even a

dilute urine may be inappropriately concentrated.

Bartter and Schwartz[1] created a hypothetical case to illustrate this point. A normal person might ingest 400 mOsm and two liters of water daily in addition to his insensible water loss. He would excrete two liters of urine a day containing 200 mOsm per liter. At the end of the day, a total of 400 mOsm in two liters of water would be excreted, the urinary concentration would be low, and water and osmolar balance would be maintained. In the presence of a small excess of ADH secretion only 1,800 ml of urine a day might be excreted. The urinary osmolality would be 222 mOsm per kg of H_2O, which is hypotonic to serum, but 200 ml of free water would be retained. If this continued day after day, SIADH would result. The point of this example is that although most patients with SIADH have highly concentrated urine, as was true in the patient presented today, concentrated urine is not necessary to make the diagnosis of SIADH. What is necessary is that the urine be inappropriately concentrated for the physiologic setting. The final criterion for the diagnosis of SIADH is continued excretion of sodium in the urine. This aspect will be discussed in more detail later.

The classic description of the SIADH was made in 1957 by Schwartz et al[2] in patients with carcinoma of the lung, in particular, oat cell carcinoma of the lung. Since this original report, a number of workers have fractionated oat cell carcinomas and isolated a substance which is immunologically[3] and physiologically[4] identical to normal human antidiuretic hormone (arginine vasopressin). Although it is not definitely known whether this results from a trapping and concentration of circulating ADH in the tumor or from the synthesis of ADH by the tumor, most workers assume that the tumor is making the hormone. Since the original descriptions, ADH-like material has been described in several other tumors as well. These tumors are of little consequence to pediatricians, but we frequently see SIADH in children in disorders involving the central nervous system, particularly meningitis.[5] It is my feeling that essentially all children with meningitis have SIADH at least in a mild form. We generally assume that this is the case and restrict fluid intake during the course of acute meningitis. SIADH is also seen in a variety of other central nervous system disorders such as head injury, brain abscess and brain tumor. SIADH also occurs in a number of pulmonary conditions such as pneumonia or tuberculosis.

What are the signs and symptoms of SIADH? In many cases there are none. The existence of clinical findings in this condition indicates that the diagnosis has been delayed. All of the symptoms of SIADH occur because the patient has water intoxication. If the diagnosis is made early, and if the serum osmolality is kept above about 240 mOsm per kg of H_2O, the patient is likely to be asymptomatic. The only way the diagnosis can be made in such a patient is by laboratory tests. This was the case with the child presented this morning. Usually the syndrome progresses no further, but occasionally symptoms do develop. The mildest symptoms of SIADH are anorexia and nausea. As the syndrome becomes more severe, personality changes develop. These symptoms usually occur when the serum sodium falls to 110 to 120 milliequivalents (mEq) per liter. If the serum sodium falls below 110 mEq per liter, neurologic signs can occur such as decreased reflexes, pronounced weakness, Babinski reflexes, stupor and, finally, convulsions and death.

The values given here relating the serum sodium concentration with symptoms are not absolute. Occasionally patients have significant symptoms at serum sodium levels above 120 mEq per liter while other patients with serum concentrations in the 105 to 110 mEq per liter range may have slight lethargy without other symptoms. The apparent explanation for this is that the rate at which dilution occurs in the patient is also important. However, the relationship of serum sodium concentration to symptoms applies fairly well in the pediatric age group because children generally have acute SIADH. In contrast, adults with oat cell carcinomas have SIADH for as long as they survive their primary disease. The syndrome is significantly different in such patients who may become hypotonic over a relatively long period of time. They often tolerate a given degree of hypotonicity better than children with SIADH who have become hypotonic more quickly.

There is no way to prevent inappropriate secretion of ADH, but therapy can prevent or minimize symptoms. There are three major forms of therapy of SIADH. The most significant of these is fluid restriction. If fluid intake is restricted to less than insensible water loss, serum osmolality will slowly rise and symptoms, if present, will disappear. In fact, it is theoretically possible to give a patient with SIADH no fluids without danger.

The second approach to therapy is the administration of sodium chloride. This is not necessary,

however, unless the child is acutely symptomatic from his hyponatremia (which usually means he is having seizures). In such a situation, it is essential to increase the serum sodium concentration more rapidly than by fluid restriction alone. These patients should be given sufficient hypertonic sodium chloride to raise the serum sodium concentration about 10 mEq per liter (mEq NaCl to be infused = .63 × body wt in kg × 10 mEq). In symptomatic patients, the infusion of hypertonic sodium can be lifesaving. If the patient is hypotonic but has no significant symptoms, sodium chloride infusion is not indicated, since such patients will excrete any sodium load given. Continued loss of sodium in the urine is one of the hallmarks of SIADH.[6,7]

At first it was thought that the hyponatremia in SIADH was a result of dilution of body fluids by the retained water. However, very careful balance studies have been done in a number of patients, especially in adults with chronic SIADH, and serum osmolality falls more than can be explained on the basis of the amount of water retained. Another possible explanation for the hyponatremia is that there is a loss of sodium in the urine. Urinary sodium concentrations in patients with SIADH are inappropriately high. When the serum sodium concentration is low, it is appropriate to have a urine sodium concentration of nearly zero, with subsequent sodium retention and correction of the hyponatremia. Patients with SIADH have a relatively high urine sodium concentration. However, if the urinary sodium loss and the water retention are both considered, the hyponatremia is still not completely explained. The question of what happens to the sodium is unanswered. The popular explanation is to say that it becomes bound in a form that is osmotically inactive (another way of saying that the sodium disappears). What this actually indicates, however, is that we do not really know where the sodium goes.

When the patients are water restricted and recover from SIADH, they lose weight and retain sodium. The rise in serum sodium concentration with recovery also cannot be explained fully by water loss or sodium retention or both. Thus, the sodium seems to "reappear" with recovery. It is useless to treat an asymptomatic patient with SIADH by giving him salt because he will excrete the sodium load in the urine over the next 12 to 24 hours. The continued excretion of salt in patients with SIADH appears to be caused by depressed proximal tubular sodium reabsorption resulting from fluid retention and concomitant extracellular fluid volume expansion. The only indication for salt infusion is a convulsing or deeply stuporous child. In such a child, sodium should be infused and then serum sodium concentration maintained by fluid restriction.

The third form of therapy is alcohol, which was tried in the patient presented. The use of alcohol is interesting physiologically. The diuretic effects of alcohol are well recognized. Alcohol decreases the secretion of ADH from the pituitary gland. The administration of alcohol in moderate amounts inhibits ADH secretion and reverses the syndrome in many but not all children with SIADH. There is no explanation for the variability of its effect. In a number of children there may be a dramatic increase in urine output after the administration of alcohol. However, alcohol does not decrease tumor-produced ADH. Therefore, the administration of alcohol in a patient with SIADH may distinguish between production of ADH by an autonomous tumor or by the pituitary.

In summary, SIADH is not a rare, esoteric condition. We see it frequently in postoperative patients and in patients with meningitis. Its symptoms are often mild because we routinely restrict fluid intake in these patients. It is, however, a potentially life-threatening problem if allowed to progress untreated. On the other hand, if the diagnosis is made early, SIADH can be a completely benign condition.

DR. SCHULTZ:* I would like to support the contention that inappropriate ADH response is quite common in meningitis and probably is the rule rather than the exception. Very likely the most common cause of inappropriate ADH seen in many hospitals is something other than meningitis, namely pneumoencephalography. A controlled series, studying pneumoencephalograms done for various conditions, showed that over half of the patients develop SIADH.

It is interesting that one may feel bad that the child lost cerebrospinal fluid and in order to replenish it one writes the almost routine orders following pneumoencephalographic studies, "Keep flat on back, force fluids." If the nurses really force fluids, this is forcing water on a child with SIADH. We wonder why some of these patients do not wake up quickly after pneumoencephalography and why they do not feel well the

*Paul Schultz, MD, Assistant Professor of Pediatrics and Neurology.

next day. I am sure this contributes to the morbidity of the procedure.

QUESTION FROM THE AUDIENCE: *What is the dose of alcohol and what are some of the other symptoms from it?*

DR. MENDOZA: The best studies on the effect of alcohol as an inhibitor of ADH secretion were done in adults in the 1940's. These volunteers were given four ounces of bourbon. I've extrapolated from that to get a dose of 1 ml of alcohol per kg of body weight, given mixed in orange juice. I've never seen anybody develop other symptoms from that dose.

QUESTION FROM THE AUDIENCE: *Is there any abnormality in aldosterone metabolism in* SIADH*?*

DR. MENDOZA: The answer is probably yes. It is a fact that aldosterone levels are low or low to normal in patients with SIADH, which could contribute to the hyponatremia and sodium loss. The importance of this in the overall pathogenesis of SIADH is unclear. The sequestering of sodium and the sodium loss in the urine can both be prevented by decreasing the fluid intake. That is, if a patient has an oat cell carcinoma and SIADH and is given water, the serum will become hypotonic. The patient will retain water, decrease proximal tubular sodium reabsorption and hide that sodium which mysteriously becomes osmotically inactive. All this can be prevented by preventing excess water intake. The aldosterone deficiency may be insignificant in the pathogenesis of the syndrome, since the aldosterone levels do not change with water restriction which prevents sodium loss.

QUESTION FROM THE AUDIENCE: *Could the sodium be in the cells?*

DR. MENDOZA: The fact is that the intracellular total cation concentration has to be quite low since intracellular osmolality always equals extracellular osmolality in the steady state. Various investigators have measured the loss not only of sodium but of potassium, calcium, magnesium, and other cations. However, it is still not possible to explain the hypoosmolality on the basis of cation loss. Therefore, there must be some cation that is unavailable to total body water in terms of its osmotic activity.

QUESTION FROM THE AUDIENCE: *Does alcohol change the sodium excretion?*

DR. MENDOZA: It does secondarily because if therapy with alcohol is successful, there is water diuresis and the normal plasma volume and total body water return. As I mentioned, when there is normal plasma volume and total body water there is no excessive salt loss in spite of the continuation of inappropriate ADH secretion. This can be shown both in patients with oat cell carcinoma and in experimental animals or human volunteers given repeated injections of vasopressin.

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Refer to: Complications of vomiting—The Boerhaave and the Mallory-Weiss syndromes—Medical Staff Conference, University of California, San Francisco. West J Med 121:50-54, Jul 1974

Complications of Vomiting

The Boerhaave and the Mallory-Weiss Syndromes

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Vomiting is basically a protective function which may even on occasion be life saving. As is the case with many such functions, however, it may carry with it its own complications ranging from the unpleasant to the dangerous. Dr. David Watts has recently reviewed a series of our patients with the Mallory-Weiss syndrome. This morning he will discuss this syndrome and other problems which may be associated with vomiting.*

DR. WATTS:† Vomiting is possibly one of the least pleasant experiences of life. If it has a positive side, it is that vomiting can on occasion relieve gastric distress and can clear the stomach of noxious or disagreeable substances. Though aesthetically somewhat wanting, it has over the ages commanded considerable attention as a therapeutic tool. Indeed, various concoctions, potions and natural spirits have been used to induce emesis in the hopes of relieving some of the abdominal woes of man. Galen, for example, recommended administering warm water and oil to patients with opium poisoning, until vomiting occurred.

Emetics commonly used in the United States at the turn of the century included some that were frank poisons themselves but were capable, fortunately, of inducing emesis before significant amounts were absorbed.

In short, vomiting has long been considered desirable under certain circumstances. It is now quite clear, however, that this violent assault upon the stomach and esophagus can result in damage to these structures, producing a wide range of lesions. These range from simple tears of the mucosa to, in the more severe circumstances, the very catastrophic, through-and-through ruptures. The Mallory-Weiss lesion is the most well known of emetogenic lesions, but it is inseparably linked with a number of other lesions that can result from retching or vomiting. These include the Boerhaave lesion, intramural hematomas, intramural perforation and gastric perforation.

Gastric Perforation

Gastric perforation is included here for the sake of completeness, though this lesion is not usually postemetic. Most cases of perforation of the stomach are due to intragastric disease processes, such as gastric ulcer or carcinoma, or are caused by trauma due to sharp penetrating missiles

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine

†H. David Watts, MD, Assistant Professor of Medicine

or severe blunt trauma to the abdomen. In a small number of patients, however, there may be a so-called spontaneous rupture of the stomach, mostly associated with vomiting or overeating or both.[1,2]

Intramural Esophageal Perforation

An intramural esophageal perforation is a lesion that occurs as a result of continued retching and vomiting which causes the mucosa to become lacerated and a small false lumen of the esophagus to be formed.[3,4] The lumen may dissect for some distance or remain relatively localized. This lesion basically can be regarded as an incomplete Boerhaave lesion, and may respond to conservative measures alone.[3]

Intramural Hematomas

Intramural hematomas were first described in the literature in 1965.[5] The most dramatic cases were reported later by Thompson, Ernst and Frye.[6] In one of their patients a dissecting hematoma encased the entire esophagus, and in another it dissected along the lesser curvature of the stomach. Both required surgical operation, and both could be traced to small mucosal lesions in the region of the cardio-esophageal junction.

A somewhat milder form of this lesion was recently reported under the name esophageal apoplexy.[7] Three patients were described, all elderly ladies with intramural hematomas occurring at the cardio-esophageal (C-E) junction. Despite the rather dramatic presentation of pain and hematemesis, and esophageal filling defect seen by x-ray studies and endoscopic examination, all three responded to conservative management.

The Boerhaave Lesion

The first description of an emetogenic lesion of the esophagus is attributed to the Dutch surgeon, Hermann Boerhaave. His report of the patient and the lesion was contained in a 70-page monograph which appeared two and one-half centuries ago this year.[8] His famous patient was the Grand Admiral of the Netherlands, Baron von Wassenauer.

It seems that the Baron was accustomed, as were others of his station, to great gastronomic overindulgence. This was sometimes followed by self-induced emesis when such practices caused him distress. He was in the habit of taking a copious draught of an infusion of "blessed thistle" and an ipecac-like substance. One evening in the late 1600's, the Baron became very distressed, for he downed three tumblersful of his favorite remedy and when it failed to work, gagged himself. He experienced sudden excruciating chest pain, saying he felt something had broken inside. He was right. When he died a short time later, Dr. Boerhaave performed an autopsy and found the esophageal perforation that now bears his name.

The Boerhaave lesion is a very predictable one. It occurs almost invariably in the distal esophagus, 1 to 3 cm above the C-E junction, is arranged longitudinally and located on the left posterolateral wall. This lesion has been easily reproduced in human cadaver esophagi tied off and blown up like a balloon until they burst.[9] However, recognizing that this was not the most physiologic of circumstances, Bodi et al[10] altered the experimental design by leaving the cadaver esophagus *in situ,* and *not* obstructing the upper esophagus. With a rapidly moving bolus of fluid injected through the cardia and out the esophagus the Boerhaave lesion could be reproduced, leading to the postulate that the sudden filling of the lower esophagus with a sizable volume of fluid caused rapid distension and rupture.

It was not until 1947 that the first successful surgical closure of a Boerhaave lesion was done.[11] Today, the increased success rate for this procedure depends on rapid diagnosis, wide debridement of necrotic esophageal and mediastinal tissue, adequate postoperative drainage and broad spectrum antibiotic coverage.

The Boerhaave lesion is regarded as the most rapidly fatal and most serious perforation of the gastrointestinal tract. An immediate chemical mediastinitis occurs, manifested by excruciating chest pain and hypotension, and may be easily mistaken for a myocardial infarction. The best route to correct diagnosis is a high index of suspicion and good x-ray studies of the chest. Mediastinal emphysema occurs early and can be auscultated over the pericardium. This sign is commonly known as Hammond's crunch. The emphysema can be seen on x-ray films in the mediastinum, or when it dissects far enough superiorly as it commonly does, it may be palpated subcutaneously above the clavicles. A left pneumothorax and pleural effusion occurs in approximately 80 percent of cases. Rupture through the pleura may occur, either immediately or later, as a result of the intense inflammatory response. Rupture into the pericardium has also been reported. The pleural fluid will show a significant

amylase activity, thus causing possible confusion with another diagnostic possibility, acute pancreatitis. The amylase in the pleural fluid of patients with Boerhaave syndrome migrates electrophoretically with salivary amylase, thus emphasizing the contribution of swallowed secretions to the genesis of the effusion.[12] Also of help in distinguishing it from pancreatitis is the fact that serum amylase activity is not elevated in patients with the Boerhaave lesion alone.

The prognosis of untreated patients is very grave. In a study by Derbes and Mitchell,[13] a careful review of survival in the era before surgery was conducted. Twenty-five percent of all patients studied died within 12 hours of the rupture, 65 percent within the first 24 hours and the remainder by the end of the week. This was at a time when good antibiotic coverage was not available, and although there are now scattered reports of nonsurgical cures, such cases still merit reporting. Hence, a misdiagnosis is almost invariably fatal. In the rare case where symptoms of mediastinitis are minimal, ingestion of water-soluble contrast media may help make the diagnosis.

Shock is not a contraindication to operation in these patients; rather, it underscores the necessity for surgical intervention, for upon opening the mediastinum and release of tamponade, blood pressure is often revived. Postoperatively, wound infection with resultant dehiscence or formation of bronchopleural fistula are the most feared complications. Therefore, adequate debridement during operation and placement of drains before closing are imperative. Despite these problems, reported survival rates range from 60 to 90 percent of cases in which operation is done.[13]

A Boerhaave lesion may on rare occasions bleed if the tear disrupts vessels of a significant size,[14] but it is not likely that confusion will arise in distinguishing it from a Mallory-Weiss lesion because of its associated signs and symptoms.

Having discussed an emetogenic lesion with rather clear surgical indications, we move to one about which there perhaps is still some controversy.

The Mallory-Weiss Lesion

The Mallory-Weiss lesion was first described in 1929. In their original paper, Mallory and Weiss[15] described 15 patients each of whom, after a long and intense alcohol debauch, developed massive gastric hemorrhage with hematemesis. During autopsy studies of four of these patients, between two and four fissure-like lesions of the mucosa of the gastric cardia were found in each. Characteristically, these lesions were arranged around the circumference of the cardiac opening along the longitudinal axis of the esophagus. Two factors were considered as causes: alcohol and vomiting. The investigators were aided in incriminating the latter by the occurrence of an identical lesion in a patient with pernicious vomiting in pregnancy.

Mallory and Weiss felt strongly that these lesions occurred only when disco-ordinate vomiting occurred. This might occur when repeated episodes of vomiting lead to "fatigue" of the vomiting center, resulting in forceful and prolonged contractions of the muscles of retching. Since we now know that this lesion may occur without repeated episodes of emesis preceding it, it is no longer necessary to rely upon this hypothesis.

A rather large number of the various causes leading to vomiting and producing the Mallory-Weiss lesion was listed by Weaver, Maxwell and Castleton in 1969.[16] Alcohol was a decided influence in 60 percent, but almost any imaginable cause for vomiting can result in the Mallory-Weiss tear, including several iatrogenic forms. It is also important to note that the lesion may be produced by factors other than vomiting that cause sudden increases in intra-abdominal pressure such as straining at stool or sudden heavy lifting, or even cardiac massage. A clear history of preceding episodes of vomiting is *not* always present. In fact, recent reports state that vomiting or retching before the occurrence of the lesion is only found in the history of some 50 percent of patients.[17,18] It appears, therefore, that in a sizable number of these patients the lesion may develop with the first episode of vomiting. This emphasizes the fact the Mallory-Weiss tear can certainly occur in the absence of a classic history.

Hiatus hernia has often been considered to be a predisposing condition to the development of the Mallory-Weiss lesion.[19] With sudden descent of the diaphragm and increased intra-abdominal pressure, intragastric pressure rises sharply. The contents of the stomach are forced upward, causing dilatation of the hiatus hernia (HH) pouch. The pouch is located in the thorax where there is less extraluminal pressure, and considerable ballooning of the pouch may occur and lead to tearing of the mucosa. The incidence of HH in the Mallory-Weiss syndrome is 50 percent, but since

a temporary hiatus hernia can be caused by retching in many "normals," this datum is not helpful. What this theory fails to explain, however, is how such lesions may occur in the distal esophagus, as around 30 percent of them do.[18] We are forced to conclude, I think, that the existing theory of the pathogenesis of this lesion is inadequate. An alternative explanation comes from the observation of retching during endoscopic examination. Depression of the diaphragm can be seen intralumenally as a constricting ring moving down a relatively stationary esophageal tube with some ballooning occurring proximally as the ring passes. Shearing forces generated by movement of esophageal mucosa through this ring may contribute to the genesis of such a lesion. Since the diaphragm commonly rests 1 to 2 cm above the C-E junction, distal esophageal tears can be explained by this hypothesis.

How does one arrive at the diagnosis of a Mallory-Weiss tear? The classic history of repeated retching will provide a clue in probably less than half of the cases. X-ray studies are not generally helpful. Sporadic cases of diagnosis from x-ray films have been reported. In these instances the radiologist was fortunate enough to catch contrast media in the Mallory-Weiss trough,[20,21] but this is the exception rather than the rule.

Endoscopy is by far the best diagnostic tool. From our experience with this disorder, recent lesions appear bloody and fresh. Those that are a few hours old will be covered by a large clot. By the third to fourth day the clot is gone, and the underlying scar tissue is apparent. There is complete healing by seven to eight days.

Standard treatment of this lesion includes lavage until clear, followed by administration of antacids. The use of tubes should be avoided. This is purely empiric therapy, and no controlled series exist to help evaluate it.

Use of a Sengstaken-Blackmore tube as a tamponading device against the bleeding site was advocated recently by Loren Pitcher,[22] but some observers have said that this might even extend the lesion.[23] It clearly adds another potentially complicating device to the regimen. For those patients in whom the bleeding does not stop, arteriography and vasopressin infusion has been used successfully by Dill and coworkers[24] to arrest hemorrhage.

It is our feeling, however, that the natural history of the lesion includes spontaneous arrest of hemorrhage in most cases and that the tip of the iceberg, obviously the most dramatic part, is what has been given the most attention.

With the advent of endoscopy the diagnosis of the Mallory-Weiss syndrome can be made with certainty. Widespread use of this technique has resulted in the appreciation of a higher frequency of diagnosis of this lesion (some 4.5 percent among all causes of significant upper gastrointestinal bleeding in some studies).[18,25] The fact that this lesion is benign in a significant number of patients has recently caught our attention and led to the observation that average blood loss is approximately two units (39 percent of 36 patients not requiring any transfusion at all), surgical intervention is necessary in 19 percent, and mortality was very low (3 percent).[18]

Thus, we have seen some changes in our conception of the Mallory-Weiss syndrome: (1) That a history of vomiting preceding hematemesis is not at all necessary; (2) that the lesion itself does not usually bleed massively; (3) the hemorrhage has a tendency to arrest spontaneously or in response to conservative medical treatment, and (4) that the mortality rate is quite low. It seems likely also that smaller, subclinical lesions commonly develop but escape detection simply because of the lack of significant symptoms. Hence, the lesion is probably a great deal more common than is realized. As a result of these observations and conclusions, we can say that conservative management is indicated until it becomes clearly apparent that medical therapeutic methods have been exhausted or until the patient's clinical course departs seriously from the natural history of the lesion.

A common remedy in the ancient writings of the Torah was a mixture of roots and herbs in beet juice which the patient was given to drink. Although it usually cured the patient, it unfortunately rendered him impotent. This example has some applicability to the Mallory-Weiss syndrome. In closing I submit that in medicine generally, and perhaps specifically in the case of the Mallory-Weiss lesion, the physician must make very certain that the cure he recommends is not inappropriate or perhaps even worse than the disease itself.

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Legal Implications of Laparoscopic Complications

LET ME JUST COVER THE HIGHLIGHTS of what might concern you in regard to laparoscopy. The informed consent doctrine applies differently in different states. Some states require more disclosures by physicians to patients than do other states in order to secure an adequately-informed legal consent. But let me try to give some minimal concept as to what probably would protect you in most states. If we can avoid considering laparoscopy as simple (and we can always avoid telling a patient it is simple) you have avoided 90 percent of the problem of informed consent. It's as simple as that. You never, never tell a patient that any laparoscopic procedure, either for diagnostic or therapeutic purposes, is simple; and you will have avoided most of the problems associated with it.

I think that all of your laparoscopic procedures should have some type of written consent form. Somewhere in the middle of the form, put the statement that this procedure, like all operative procedures, may be subject to serious complications or even death. You can use that language somewhere in the middle of your form. Now, I am not telling you to list all of the complications. I'm not telling you not to, either. But if that is the minimal disclosure required, I don't think it is going to harm many patients. First of all, they have to read it. Second of all, they have to understand it. And most patients realize the generalities of "serious complications or death." And as long as there is evidence of some type of disclosure on a minimal basis such as that, I think you've avoided another 9 percent of the problem, in addition to the 90 percent avoided by not telling them it's simple. If there is any question concerning the indications for the procedure, then you have to go farther. There's no way of justifying the performance of a non-indicated procedure without the patient's knowing it's not indicated . . . or without the patient's knowing that there are questions concerning its indications. If that's true, then you've got to disclose it and go further in terms of the risks involved, so that the patient is then making a decision along with you as to whether the procedure should be performed at all . . ."

—DON H. MILLS, MD, JD, *Los Angeles*

Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 21, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Important Advances in Clinical Medicine

Epitomes of Progress—Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities
California Medical Association, 731 Market St., San Francisco, CA 94103

Immunological Defenses in Cancer

THERE ARE MANY SIMILARITIES between the human body's defenses against intracellular infections (tuberculosis, toxoplasmosis, fungi and many viruses) and its defenses against cancer. The two types of immunological defense against infection and cancer are cellular and humerol.

Cellular immunity depends on specifically sensitized lymphocytes which can kill the sensitizing cancer cells specifically. After combining with the antigenic tumor cell, lymphocytes may (1) kill by contact, (2) release factors (lymphokines) which kill cells nonspecifically and (3) induce production of activated macrophages. Once macrophages are activated, they can kill intracellular organisms or tumor cells nonspecifically. Activated macrophages are important in protection from diseases such as toxoplasmosis and tuberculosis, as well as cancer. Macrophages may be activated by a variety of factors such as bacille Calmette Guérin (BCG), chronic toxoplasmosis and endotoxin. Several studies indicate that BCG vaccination in large numbers of children may decrease future rates of mortality from leukemia.

Recent studies indicate that most cancer has tumor specific antigens. Release of small quantities of these antigens, as from slow growing cancers, may induce both circulating immunoglobulin antibodies and cytotoxic lymphocytes. If a large quantity of tumor antigen is released, the sites of antibody production may be overpowered and immunological paralysis ensues. In these cases the cancer may continue to grow rapidly. Soluble tumor antigen may also combine with cytoxic lymphocytes to neutralize them, which is a frequent occurrence in late cancer.

If the immunological response to the tumor antigen is principally circulating noncomplement binding immunoglobulin antibodies, these may coat the surface of the tumor cells and block the cytotoxic effects from any subsequent antitumor lymphocytes. Development of cancer immunity might best be obtained by methods which minimize the production of noncomplement binding immunoglobulin antibodies and encourage the delayed immune system to produce specific antitumor lymphocytes, and possibly to produce complement binding antibodies which may also kill cancer cells.

As in many types of infection (that is, intracellular) the tumor may persist if it is in a portion

of the body away from ready access to antibodies. Immunological defenses are much less effective in large tumors, as antibodies cannot reach the inner malignant cells. Therefore, immunological defense in cancer (immunosurveillance) is much more effective in the beginning stages of cancer or after most of the tumor mass has been removed by surgery, radiation or chemotherapy. Unfortunately, the latter two modes of therapy may cause a pronounced reduction in the patient's immune capacity.

The human body is probably faced with numerous neoplastic mutations, but rarely develops clinical cancer. The successful operation of the nonspecific and specific immune system is probably largely responsible for this level of protection.

Research in this area has produced a number of recent advances in our understanding of cancer immunology. It is anticipated that this new knowledge will add to and modify the information in this epitome.

WILLIAM D. MCKEE, MD

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Indoor Air Pollution: Effects on the Non-Smoker of Tobacco Smoke Indoors

Smoke from an idling cigarette, "sidestream smoke," contains almost twice the tar and nicotine as does smoke inhaled while puffing on a cigarette, "mainstream smoke."

Furthermore, the carbon monoxide in the air near a smoker can be increased from an atmosphere value of perhaps one to three parts per million (ppm) to transient peaks exceeding 90 ppm. Two other components of any tobacco smoke are hydrogen cyanide and nitrogen dioxide. The latter, an acutely irritating gas, exists in cigarette smoke in amounts 160 times greater than levels considered safe for extended exposure.

Thus, the tobacco smoking minority of our population is the source of a unique and hazardous form of indoor air pollution which can best be discussed by using such special terms as *sidestream, mainstream* and *passive* smoking. Tobacco smokers who smoke indoors clearly put upon their more numerous non-smoking colleagues by worsening allergic rhinitis, bronchitis, asthma and other respiratory diseases.

Passive smoking by the non-smoker in a poorly ventilated room or car has been shown to result in carboxyhemoglobin levels well within the range known to cause impairment of visual acuity and faulty time interval discrimination. It is possible that such levels could be lethal for the bystander who suffers from arteriosclerotic heart disease. It is no cause for wonder, then, that the Surgeon General of the United States has declared a Bill of Rights for the non-smoker.

WILLIAM J. SAYER, MD

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Coexistence of Asthma in Children with Cystic Fibrosis

A CHILD with such recurrent, chronic symptoms as cough at rest or exertion, wheezing, fever, dyspnea or nasal obstruction may well have asthma, cystic fibrosis or both. This similarity of symptoms is a reflection of similar responses to the pathophysiology involved in both diseases.

It is well known that bronchial obstruction in patients with asthma is due to bronchoconstriction, submucosal edema, and increased bronchial secretions, and that patients with cystic fibrosis have highly viscid secretions. What is usually not appreciated is that nearly 50 percent of children with cystic fibrosis have exercise-induced bronchoconstriction and that a significant number have improved pulmonary function after inhalation of the bronchodilators epinephrine and isoproterenol. Therefore, bronchoconstriction as well as abnormal bronchial secretions, play a role in the clinical symptoms of both asthma and cystic fibrosis.

Asthma has been reported to occur in 7 to 10 percent of children with cystic fibrosis. This is similar to the incidence of asthma in the pediatric population in the United States. Therefore, it is important to realize that in some patients, both cystic fibrosis and allergy may be causing the symptoms and that treatment for both is necessary.

Recently, Caplin et al found interesting similarities between aspirin-induced asthma and cystic

fibrosis. These include high incidence of nasal polyps, severe intractable pulmonary disease with wheezing, and serum and sputum factors which inhibit ciliary action. Further identification of this inhibitor may shed light on the pathogenesis of both diseases.

MICHAEL FRANZ, MD
STANLEY P. GALANT, MD

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Genetics in Atopy

THE HEREDITARY NATURE of atopic allergic states, such as hayfever, asthma and eczema, has been known for half a century. Vaz and Levine discovered that gamma E immunoglobulin (IgE) antibody production in inbred strains of mice was under two sets of genetic controls. One causes elevated serum IgE antibodies to many antigens and the second controls reagin-production response to only certain antigens. The latter, termed an Ir (immune response) gene was linked closely to the H-2 major histocompatibility locus in mice. Such Ir genes described earlier by McDevitt and Benacerraf responded to synthetic polypeptides or minute doses of protein antigens.

Levine et al noted that the protein antigen dosage of pollens that one person inhales during a whole pollen season is extremely small, for example, 1 μg of ragweed antigen E (AgE) during a three-month ragweed season in New York. They wondered if there was an immune response gene in certain persons which could respond with IgE production to ragweed AgE. In seven families with a propositus and several other members with ragweed hayfever, they found that persons with clinical hayfever and intense wheal and flare skin tests to ragweed AgE all had the same HL-A histocompatibility haplotype which they called the "hayfever haplotype." There was, however, no single common "hayfever haplotype" in the seven families. Of 26 members of the seven families with the "hayfever haplotype," 20 had clinical hayfever and positive ragweed AgE skin tests. None of 11 family members who had the other haplotype of the propositus (and lacked the "hayfever haplotype") had clinical hayfever. These results were highly significant statistically ($p<.01$). Furthermore, none of 20 family members with neither haplotype of the propositus had hayfever. The close association between HL-A haplotype, clinical hayfever, and IgE antibody production in successive generations in man resembled the immune response gene associated with H-2 histocompatibility loci in mice. These findings suggest that tissue typing of infants born into allergic families might identify those at risk from allergic disease.

Marsh et al surveyed a population of 105 unrelated ragweed sensitive patients with positive findings for ragweed AgE from skin and leukocyte histamine release tests. Seventeen of these patients were highly sensitive to a minor antigenic determinant of ragweed called Ra5 (molecular weight 4,700), 77 percent were Ra5-insensitive and ten had intermediate sensitivity. HL-A typing of this population showed a highly significant correlation between HL-A7 and closely related group tissue types and high sensitivity to Ra5 ($p<0.003$) relative to frequency of those tissue types in the Ra5-insensitive group. This suggested to them that a certain immune response gene located at or near an HL-A locus controlled the immune responsiveness of a person to ragweed Ra5.

Hamburger and Bazaral at the University of California, San Diego, reported that total serum IgE levels in 26 pairs of monozygotic twins were very close, while IgE levels in dizygotic twins varied as greatly as in the general population. They suggested that serum IgE level is controlled genetically, as in Levine and Vaz's first group of mice.

Intensive efforts are underway in many laboratories for a better understanding of the familial occurrence of allergy on the basis of immune response genes.

OSCAR L. FRICK, MD

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Immune Mechanisms and Infertility

THREE IMMUNE MECHANISMS are currently considered to be causes of human infertility. These include autoimmunization in men and the formation of both circulating and tissue antibodies against semen in women. In men, an immunoglobulin G in plasma has been shown to cause agglutination of spermatozoa. In women, a circulating immunoglobulin G has immobilized spermatozoa, while immunoglobulin A in cervical mucus has agglutinated spermatozoa. The antigen responsible for these immune responses has not yet been identified, though it may be one of several proteins present in seminal plasma. One possibility is lactoferrin which, in addition to being present in seminal plasma, also coats the spermatozoa. Clinically, an immunological examination is indicated in problems of infertility when results of routine tests are normal.

W. LESLIE G. QUINLIVAN, MD

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Indications for Measuring Serum IgE Levels

MEASUREMENT OF SERUM IgE is now available both commercially for high levels and, for a wider range of concentrations, at several research and hospital immunology laboratories. While a grossly elevated serum IgE level is neither necessary nor sufficient for the manifestations of atopic disease, the *probability* of "allergic" symptoms being due to IgE-mediated hypersensitivity is highly correlated with the serum IgE level.

This is shown in the following analysis:

IgE units/ml*	*Theoretical Percent Atopics in an unselected population*
0-100	5
101-350	18
351-700	30
>700	100

*WHO IgE unit = approx. 2.4 ng IgE.

Atopic disease is rare at serum IgE levels of less than 100 units per ml and increasingly probable in persons with elevated IgE levels. Measurement of the serum IgE level is therefore a useful ancillary tool for the diagnosis of atopic eczema, urticaria, rhinitis, asthma and bronchopulmonary aspergillosis. An early rise of serum IgE level in babies is significant and is associated with atopic disease; however, special techniques are required for assay of the low levels observed. High levels are seen in many, but not all, cases of helminth infestation and in Wiskott-Aldrich syndrome. Extremely low levels (<15 units per ml) are seen in non-allergic babies, in many normal children and adults, and in certain immune deficiency diseases.

In other pathologic conditions IgE levels are elevated too inconsistently to be of diagnostic aid.

H. ALICE ORGEL, MD, PH D
ROBERT N. HAMBURGER, MD

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The Role of Small Airways in Asthma

WHICH AIRWAYS in the lung are constricted in an asthmatic attack? Until recently it was assumed, based upon autopsy findings, that the major site of obstruction was in very small airways—primarily the bronchioles. Further, it was thought that these small airways constricted in an attack to an extent proportional to the severity of the episode.

Recent studies indicate that these concepts were, at least, incomplete. Bronchoconstriction has been found to be present in some areas of the lung but not in adjoining areas. This variation in regional function accounts for the common presence of hypoxemia in asthma. Another "nonclassical" finding is that large airways—bronchi—are often noted to be greatly reduced in caliber during bronchographic studies. Finally, increased airway resistance, always found during asthmatic attacks, has been shown to be primarily due to constriction of airways of 3 mm or more (at least of moderate size).

However, these findings do not mean that small airways are normal in asthmatic subjects.

A variety of new methods (including maximal flow-volume curves and measurement of closing volume) show that small airways, probably including bronchioles, are obstructed in many asthmatic subjects.

Therefore, the site of obstruction in asthma is complex and variable with regional involvement of bronchi and bronchioles occurring in individual cases.

A. F. WILSON, MD, PH D

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Cromolyn Sodium: A New Drug for the Treatment of Atopic Allergic Disorders

RECENTLY, cromolyn sodium (Intal®, Aarane®) has been released by the Food and Drug Administration as a new agent for the treatment of bronchial asthma. It is the first major advance in the pharmacological management of asthma since the advent of the corticosteroids. Further studies of this drug have confirmed earlier reports of its prophylactic value in preventing allergen and exercise-induced bronchospasm.

The drug is administered by inhalation as a powder and purportedly is effective by preventing the release of histamine and slow-reacting-substance of anaphylaxis (SRS-A). The dose for adults and children over five years of age is the same, 20 mg inhaled four times daily. It has no bronchodilator, anti-inflammatory or anti-mediator activity. Cromolyn is ineffective in the treatment of acute attacks of asthma, including status asthmaticus. Although it is not possible to predict which specific patients will respond satisfactorily to cromolyn, children, especially those known to be hypersensitive to extrinsic allergens, are more likely to respond favorably. Most patients respond to cromolyn within a few days; occasionally it may take a couple of weeks before an effect becomes apparent. Its primary indications are (1) as a corticosteroid sparing agent in corticosteroid dependent patients and (2) as an adjunct for severe chronic intractable asthmatic patients who are uncontrolled by the usual therapeutic measures. The amount of corticosteroid drugs can usually be reduced and in some cases eliminated, but the corticosteroids should never be abruptly discontinued.

Few adverse effects have been noted with its use; however, maculopapular rashes, urticaria and other hypersensitivity reactions have been infrequently reported. Occasionally patients experience transient coughing or bronchospasm following inhalation of the drug, necessitating the concomitant administration of a bronchodilating agent or discontinuing the drug.

Preliminary investigative results have suggested cromolyn may also be useful as a topical agent for the treatment of allergic rhinitis and allergic conjunctivitis.

SHELDON SIEGEL, MD

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Falliers CJ: Cromolyn sodium (Disodium cromoglycate). J Allerg Clin Immunol 47:298, 1971

Importance of Autonomic Nervous System Control of Airways in Bronchial Asthma

IN 1931, Francis Rackemann described asthma as being like a loaded gun with a great variety of triggers that can fire the charge. A convincing explanation of this point comes from important recent advances in our understanding of the control exerted by the autonomic nervous system on the tracheobronchial tree. The normal tone of the airways is thought to be modulated by the balance of bronchodilator receptor (beta adrenergic) and bronchoconstrictor receptor (alpha adrenergic and cholinergic) stimulation of bronchial smooth muscle.

The classic concept of bronchial asthma as being solely an allergen-induced immunologic disease cannot adequately explain the exaggerated bronchoconstrictor response caused by many nonimmunologic stimuli in these patients. These factors include infection, inhaled irritants (citric acid, sulfur dioxide, carbon dust), physical agents (cold air), chemical mediators (histamine, slow reacting substance, kinins and acetycholine) and emotional effects. Szentivanyi has advanced the theory that beta adrenergic blockade is the unifying pathogenetic mechanism in asthma. This concept proposes an imbalance of autonomic nervous system receptor function due to a defective beta adrenergic receptor. The effect is exaggerated alpha adrenergic and cholinergic responses to both immunologic and nonimmunologic stimulation. Metabolic and pulmonary function studies

in asthmatics and beta adrenergic blocked (propanalol treated) normal subjects support this concept.

The beta adrenergic receptor is thought to be the cell membrane bound enzyme adenyl cyclase, which when stimulated causes an increase in cyclic 3′, 5′ adenosine monophosphate (CAMP). Increasing CAMP has been found to relax bronchial smooth muscle and inhibit release of histamine and slow reacting substance from human lung tissue. Recently, decreased lymphocyte CAMP levels were found in persons with severe asthma.

Bronchial asthma, therefore, can be viewed as a hyperreactive state of the airways resulting from an imbalance of the autonomic nervous system. Drug therapy is aimed at correcting this defect by increasing intracellular CAMP levels in an attempt to restore the balance.

LOULA AMIN, MD
STANLEY P. GALANT, MD

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Use of Intravenous Isoproterenol in Unresponsive Status Asthmaticus

ISOPROTERENOL, which is structurally similar to epinephrine, is primarily a beta adrenergic stimulator. Therefore, its major effects are bronchodilation, decreased peripheral vascular resistance, and increased rate and contractility of the heart. Isoproterenol is commonly administered by inhalation in the treatment of acute asthma. It is also frequently used intravenously in the management of atrioventricular block and similar cardiac abnormalities in a dose range of 0.01 to 0.1 μg per kilogram of body weight per minute. Recently, isoproterenol given intravenously has also been found to be effective in the treatment of status asthmaticus. However, the amounts used have been much more massive than those found effective in treating cardiac arrythmias. Wood et al were successful in treating 17 of 19 children in respiratory failure secondary to asthma using intravenously administered isoproterenol. Therapeutic effects were obtained with doses of 0.08 to 2.7 μg of isoproterenol per kilogram of body weight per minute. The possibility of avoiding the use of intubation and respirator therapy in children with status asthmaticus, who are in respiratory failure, makes this mode of therapy very attractive.

The major complication seems to be cardiac arrythmias. One of the children in Wood's series did develop tachycardia and ventricular arrythmias, necessitating discontinuation of the drug.

Increased hypoxia is a well known occurrence when isoproterenol is given by inhalation. Although hypoxia was not found when the drug was given intravenously, increased ventilation perfusion abnormalities have been reported during isoproterenol inhalation.

Intravenously given isoproterenol may have a place in the treatment of respiratory failure secondary to asthma in children. However, such therapy should be approached with extreme caution and should include adequate monitoring of blood gas, as well as cardiac and vital signs. Time and more experience will clarify the role of intravenously administered isoproterenol in the treatment of asthma.

RICHARD DAVIS, MD
STANLEY P. GALANT, MD

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Knudson RJ, Constantine HP: An effect of isoproterenol on ventilation perfusion in asthmatic versus normal subjects. J Appl Physiol 22:402, 1967

Status of a New In Vitro Test: RAST

THE RADIOALLERGOSORBENT test (RAST) for measuring IgE antibodies to specific allergens was developed by Wide, Bennich and Johansson as an outgrowth of their studies on the first recognized IgE myeloma protein. IgE was previously shown by Ishizaka to be associated with the reaginic antibodies characteristic of atopic allergy, and the RAST procedure is the best method presently available for quantitating antibodies of the IgE class. In brief, the technique uses an excess of allergen chemically bound to a cellulose disc. The disc is incubated with serum and specific serum antibodies become attached to the disc after which all other antibodies and serum proteins are washed away. Then, purified radiolabelled rabbit antibodies to IgE are added. These bind to the disc in proportion to the amount of IgE antibody in the serum.

Studies employing the RAST procedure have taught us that IgE antibodies generally increase in allergic subjects during natural exposure to seasonal pollens and that there is an apparent

decrease in antibodies following hyposensitization therapy. In general, those patients with the most strongly positive results to skin tests have the highest levels of IgE antibodies to that allergen, and subjects who have negative skin responses have low or undetectable levels of antibody. RAST has certain advantages over skin tests. For example, it can be used when skin testing is impossible or unreliable, such as when a patient has widespread dermatitis or dermographism or when a patient is receiving antihistamines, adrenergic agents or theophylline derivatives for control of symptoms. These drugs may inhibit skin responses but do not interfere with RAST. There is no risk of inducing anaphylaxis with the simple venipuncture required for RAST assays. The latter may also be more acceptable to the young patient than a large number of skin tests. RAST results are more quantitative than skin tests, and several serum specimens obtained from the same subject at different times may accurately be compared to one another or to specimens of other patients, in contrast to the difficulty one encounters in comparing skin tests done on the same person at different times or those done on different patients. RAST assays may also be adapted to the study of allergen purity and potency, providing for the first time an *in vitro* technique which has great promise in the standarization of commercial allergen preparations.

In spite of these significant advantages, the use of RAST assays is not without problems. The first is that considerable immunochemical expertise is required to properly prepare the necessary reagents and to establish reliable controls and standards. Secondly, one may encounter a problem of IgG antibody interference with IgE antibody binding when sera from patients who have been on hyposensitization therapy are tested. Finally, RAST assays are more expensive than are skin tests. Nevertheless, it appears that RAST assays are here to stay and will prove helpful in the evaluation of a limited number of patients. At present, properly performed skin tests are to be preferred to RAST assays for the routine allergy workup.

Some provision for third-party quality control of laboratories performing RAST assays on a commercial basis would be desirable since this is an area where scientific accuracy is essential in order to protect both the physician and his patient from misrepresentations.

DOUGLAS C. HEINER, MD

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EDITORIAL

Adversaries in Patient Care

ELSEWHERE IN THIS ISSUE is a timely commentary on the Medicaid experience in California in the program known as Medi-Cal. There is much to be learned from this experience and it can only be hoped that its lessons are being heeded by those responsible for designing the program of national health insurance which sooner or later will be made available to or imposed upon the people of this nation, depending upon how the law is finally written.

One of the points made by Roney in his commentary on Medi-Cal is that for any such program to work it must first be inherently workable and then there must be incentives for cooperation and a desire on the part of all concerned to make it work. The Medi-Cal program is unusual in that it was initially sponsored by organized medicine which subsequently did everything in its power to make it work, but continually found itself in an adversary position with the State administration of the program. In desperation it finally took the State itself to court in behalf of patients who had been administratively deprived of their rightful benefits under the law. The case was won but the adversary relationship continues. This has proven frustrating, costly and inefficient, and it has adversely affected patient care under the program.

There is now a generally held opinion that some form of national health insurance is both desirable and necessary. Although low in the public's assessment of national priorities, it seems destined to be bullied or jockeyed into being by the Administration and the Congress during a time of unprecedented economic inflation and unprecedented popular distrust of government. The evident absence of working health care professionals, representative of their constituencies, at the apparently substantive discussions now going on behind closed doors, reduces the likelihood of anything approaching enthusiastic support by health care professionals for whatever program emerges and presumably is enacted into law. If experience with other federal health care legislation is any criterion, the program will probably not achieve its objectives, will be costly and inefficient, and will perhaps not even be workable. All of this sets the stage for another adversary rather than cooperative relationship between those who will be administering the program after it is enacted and those who must try to deliver care to patients within it.

This does not bode well. The all-important human factors in such a human undertaking as providing for health care, such as motivation and satisfaction for those providing and receiving the care, seem not to have been taken into much, if any, account. And tragically once again it will be the patients who will inevitably bear the main brunt of it all, as was the case with Medi-Cal. It is also tragic that many of the difficulties which undoubtedly lie ahead could almost certainly be prevented even at this late date if the adversary approach, which unfortunately seems to be the order of the day, could be replaced by honest and genuine cooperation on the part of all concerned.

Unfortunately this seems most unlikely in the present climate.

—MSMW

"Inappropriate" Versus "Appropriate" Antidiuretic Hormone Secretion

IN THIS ISSUE of THE WESTERN JOURNAL OF MEDICINE Drs. Mendoza and Keller have discussed the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and suggest that varying degrees of severity of this syndrome occur frequently in pediatric patients suffering from meningitis.

When considering SIADH several important questions arise with respect to pathogenesis, diagnosis and management in either the adult or pediatric population. What is "appropriate" and what is "inappropriate" secretion of antidiuretic hormone (ADH)? The authors emphasize that changes in plasma osmolality and volume status are two "physiologic stimuli for ADH release." Should these two circumstances then be considered the two main instances whereby "appropriate" secretion of ADH occurs? From a teleological point of view, both of these circumstances have goals which tend to preserve important

aspects of body integrity, namely constancy of osmolality and volume of body fluids. Perhaps they then deserve the classification as "appropriate" stimuli of ADH release.

What then about ADH release in response to emotions, pain, trauma and exercise? Should these be considered "inappropriate" stimuli for ADH release because they do not appear to serve any immediate function in preserving total body fluid homeostasis? What also about the impaired water excretion which may be associated with adrenal insufficiency, cardiac and hepatic failure and is probably related, at least in part, to increased release of vasopressin? With adrenal insufficiency a teleological goal could be prescribed since hypovolemia may be present, but patients with hepatic and cardiac failure generally have an excess of total body fluid. Thus, a common pathway for these varied circumstances, in which non-osmotic release of ADH occurs, does not seem to be readily apparent.

A recent series of investigations, however, suggest that autonomic neural pathways may be primarily involved in the non-osmotic release of ADH.[1-5] Specifically, parasympathetic afferent pathways from the carotid sinus and aortic arch baroreceptors have been recently shown to mediate the effects of alpha- and beta-adrenergic stimulation on vasopressin release.[4,5] Moreover, diminished parasympathetic afferent tone has been shown to mediate the effect of bilateral cervical vagotomy to stimulate vasopressin release.[3] On the background of this recent experimental evidence, it is interesting to note that many of the non-osmotic stimuli for vasopressin release might be expected to be associated with increased sympathetic tone and thus diminished parasympathetic tone. In this regard, emotional stress, pain, trauma, exercise, hypovolemia, hepatic and cardiac failure, and adrenal insufficiency might be expected to be associated with enhanced sympathetic activity.

From an evolutionary viewpoint, could then the non-osmotic release of ADH be an integral part of the autonomic neural response of the organism to a variety of stress reactions? In earlier, sea-dwelling species in which water conservation was less critical, perhaps the pressor rather than the antidiuretic action of vasopressin was more important. In the context of this hypothesis perhaps all non-osmotic release of vasopressin from the hypothalamo-neurohypophyseal tract constitutes an integral component of an "appropriate" response of the autonomic nervous system to various stress reactions. Perhaps, then, only release of ADH-like activity from tumors should be classified as "inappropriate."[6]

Turning away from these hypothetical comments about the pathogenesis of SIADH, a few perhaps more practical remarks about diagnosis and management of this entity seem appropriate. In Dr. Keller's presentation she states that by day five the patient's urine and serum osmolality became "appropriate." Again, there is danger here in the use of the word "appropriate." Serum osmolality was decreased on day five to 257 milliosmols (mOsm) per kg, a level which should not be necessary to suppress ADH release and allow maximal urinary dilution. Thus, the response of this infant was not "appropriate" on day five and evidence of continued fluid accumulation and progressive hypo-osmolality from day one to five was present. In this regard, adults who are psychogenic or compulsive water drinkers may ingest 10 to 15 liters of water daily. Despite this large fluid intake, hypo-osmolality does not develop because of the exquisite sensitivity of the osmoreceptor to suppress ADH with small (2 to 4 mOsm per kg) declines in plasma osmolality.[8] The continued presence of hypo-osmolality to a level of 257 mOsm per kg in this infant then provides evidence for continued malfunction of the osmoreceptor-ADH mechanism.

Could this infant have had a so-called "reset" osmoreceptor rather than SIADH? For example, the sensitivity of the osmoreceptor may have been preserved but may have sensed 257, rather than 270, mOsm per kg as hypo-osmolality. Alternatively, the sensitivity of the osmoreceptor may have been diminished or "sluggish" in such patients so that ADH was suppressed only in the presence of large decrements (10 to 15 mOsm per kg) in plasma osmolality. Studies are needed in such patients, whose urine is diluted only when profound hypo-osmolality is present, to distinguish between "reset" and "sluggish" osmoreceptors.

The interpretation of urinary sodium concentration and excretion in patients with SIADH has also led to some confusion. Volume expansion secondary to water retention may indeed lead to increased sodium excretion and some negative sodium balance.[6] However, balance studies have shown that the fall in plasma sodium concentration in SIADH is accounted for to a negligible degree (2 to 3 milliequivalents [mEq] per liter) by

the negative sodium balance.[9] As Dr. Mendoza indicates, hypertonic saline, therefore, is not the treatment of choice in SIADH but rather a negative water balance is the goal. In chronic cases of SIADH water restriction is the preferred method of treatment. Recently, it has been shown that even with acute, symptomatic hyponatremia, hypertonic saline need not be used. The therapeutic approach described is to rapidly increase free-water clearance and correct hyponatremia by inducing diuresis with furosemide, as the urinary electrolyte losses are concomitantly replaced by a parenteral hypertonic infusion.[10] Such an approach avoids further volume expansion in patients with SIADH who already have an excess volume of total body fluids. Moreover, as Dr. Mendoza emphasizes, in the presence of this volume expansion the hypertonic saline load will be rapidly excreted.[6]

Since volume status, and not serum sodium concentration, is the main determinant of urinary sodium concentration and excretion, the authors' statement, "when the serum sodium concentration is low, it is appropriate to have a urine sodium concentration of nearly zero, with subsequent sodium retention and correction of the hyponatremia," is misleading. Urinary sodium concentration in patients with SIADH, as in normal subjects, can reach zero to 1 mEq per liter when their intake of sodium is restricted.[9] The high urinary sodium concentration in patients with SIADH is primarily related to the fact that their sodium intake must be excreted in a small volume of urine and thus necessitates a high urine sodium concentration. It is therefore important to re-emphasize that the primary defect in SIADH is that of water retention and thus, until inhibitors of ADH are available, a negative water balance achieved either by water restriction or diuretic-induced free-water losses would seem to be the most "appropriate" means of treatment. Since the role of a negative sodium balance in the pathogenesis of the hyponatremia of SIADH is negligible, the use of hypertonic saline in the treatment would seem "inappropriate."

ROBERT W. SCHRIER, MD
Professor of Medicine
Head, Division of Renal Diseases
University of Colorado Medical Center, Denver

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The Impact of Recent Findings Concerning Vitamin D Metabolism on Clinical Medicine

PERHAPS ONE OF THE most important medical advances in the last decade is the discovery that vitamin D must be converted to a hormone or hormones before it can carry out its known functions. The only known hormone produced from vitamin D is 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$) but others may follow in view of the multiple activities of vitamin D. Of great importance is the fact that $1,25(OH)_2D_3$ production is feedback regulated by both serum calcium and serum phosphorus concentrations either directly or indirectly. The serum calcium regulation is mediated by the parathyroid glands with the parathyroid hormone stimulating synthesis of $1,25(OH)_2D_3$. The actual cellular or molecular mechanism of the regulation is not understood at the present time but at least it is important to realize that serum calcium and serum phosphorus feedback controls the synthesis of a hormone ($1,25[OH]_2D_3$) whose responsibility is to elevate the concentration of these ions in the plasma. Additionally, it must be recognized that regulation of the 25-hydroxyvitamin D_3-1-hydroxylase does not take place in vitamin D deficiency.

The article by Coburn and his associates discusses the regulation of $1,25(OH)_2D_3$ production but the picture presented is not clear and it is uncertain whether these authors believe that parathyroid hormone is an important regulator, a concept firmly held by a number of investigators in the field. This is particularly an important concept in

view of the fact that 1 μg per day of $1,25(OH)_2D_3$ (50 units by Coburn et al definition) is effective in maintaining serum calcium of hypoparathyroid patients in the normal range provided dietary calcium is adequate.

The molecular and cellular mechanisms whereby $1,25(OH)_2D_3$ elevates calcium and phosphorus in the plasma by increasing intestinal calcium transport or bone mobilization are far from understood. Wasserman and his colleagues have made an important contribution to this area in demonstrating the existence of calcium binding protein in intestine which appears in response to vitamin D. Beyond that, little is established and it is of some concern that the action of $1,25(OH)_2$-D_3 is assumed to be like that of such steroid hormones as estrogen, aldosterone and testosterone. Although this may prove to be the case, it is prejudicial to assume it. Chemically vitamin D may be classified as a steroid only because it is derived from a precursor which possesses a steroid nucleus. However, structurally the resemblance of $1,25(OH)_2D_3$ to a steroid is vague at best. Whether some or all of the actions of 1,25-$(OH)_2D_3$ are mediated by nuclear interaction is also not known. It is, therefore, essential to keep an open mind regarding the mechanism of 1,25-$(OH)_2D_3$ action until clearly definitive results are obtained.

The potential clinical importance of 1,25-$(OH)_2D_3$ and 25-OH-D_3 and their analogs is indeed obvious in such diseases as renal osteodystrophy, vitamin D dependency disease, hypoparathyroidism and Dilantin®*-phenobarbital induced bone disease. Furthermore, other bone diseases and disturbances of calcium metabolism may be related to disturbances in vitamin D metabolism or at least may be benefited by treatment with vitamin D metabolites. In the article by Coburn et al attention is paid to a number of these diseases and their potential relationship to vitamin D metabolism. These considerations are important, suggestive and very much worthy of thoughtful consideration. In addition, the article represents an attempt to provide information on vitamin D metabolism to the clinician. Although very useful, there is a Southern California bias to the article with omissions of some papers which bear on such important matters as biological activity of $1,25(OH)_2D_3$ and its analogs. However, all review articles have in them blind spots, prejudices and omissions and the readers are urged to examine a variety of reviews by various authors to gain a balanced perspective of this potentially important clinical area.

*diphenylhydantoin.

H. F. DeLuca, ph d
Department of Biochemistry
College of Agricultural and Life Sciences
University of Wisconsin-Madison

Top Flight Brains for Medicine

A career in medicine appears to be the goal of an unprecedented number of college students. Exact figures are difficult to come by, partly because career goals for many students often change before, during and after college, and partly because most colleges and universities have no accurate means of determining who is a committed premedical student and who is not. But an informal survey of some of the leading universities in the West indicates they believe that as many as ten percent of their college undergraduates are pointed toward careers in medicine. This is an awesome number, and an awesome responsibility for the colleges and universities to try to provide the amount and kind of instruction this number of students expect and believe they need. And it is dismaying to realize that only a small proportion of these students, even the highly dedicated and determined, will ever achieve their goal of becoming physicians.

For medicine, it means that medical schools will have several fully qualified applicants for each position in the first-year class and the likelihood is that those who are accepted will be more than fully qualified. They will have top flight brains, as well as dedication and determination. All this is happening at a time when many physicians in practice take a dim view of the future of medicine and what they foresee as the result of increasing government intervention in medicine and patient care. The new generation apparently does not see this as a deterrent. Rather it seems likely that their intelligence, vigor, independence and determination will turn out to be more than a match for any clumsy and sluggish governmental bureaucracy with which it is likely they will have to deal.

Thus it appears that medicine will have more than its fair share of top flight brains for the foreseeable future, and this surely augurs well for patient care and for the practice of medicine.

—MSMW

CASE REPORTS

Refer to: Rhame FS, Werner SB: Vibrio parahaemolyticus gastroenteritis from eating conchs. West J Med 121:66-68, Jul 1974

Vibrio Parahaemolyticus Gastroenteritis from Eating Conchs

FRANK S. RHAME, MD, *Stanford*
S. BENSON WERNER, MD, *Berkeley*

VIBRIO PARAHAEMOLYTICUS was first recognized as a cause of human gastroenteritis in 1950 in Japan.[1] It is now recognized as one of Japan's most common causes of foodborne illness.[2-4] In the warm summer months it accounts for up to 50 percent of cases. The organism is widely distributed in the coastal waters of the world, including many areas of the United States. It has been found in a variety of marine fish, shellfish, mud, sediment and water samples obtained primarily from offshore locations. Soft tissue infections[5] caused by V. parahaemolyticus have occurred, but most disease and all outbreaks have been limited to gastroenteritis caused by contaminated seafood. In 1971 it was confirmed as a cause of foodborne illness in the United States.[6] In the 13 outbreaks reported from this country to date, cases have been traced to contaminated oysters, crab, shrimp, and lobster.[7] The present case may have originated from conch meat taken from waters near the Bahamas; it is the first time that this disease has been confirmed in California.

Report of a Case

A 38-year-old black housewife was admitted to hospital February 20, 1973, because of watery diarrhea and lower abdominal cramps. Symptoms had begun 23 hours after she had eaten from conchs which had originated in the Bahamas and had been bought at a Miami fish market. The conchs had been packed in ice, air freighted to California and eaten the day they were received. The patient's lower abdominal pain was sudden in onset and was followed shortly by profuse watery diarrhea and vomiting. She denied chills, headache and myalgias. In the 48 hours before the onset of symptoms, she had eaten only dry or canned foods except for Polish link sausage.

On admission, she was in minimal distress. Temperature was 36.6° C, pulse 84 and regular, blood pressure 140/100 mm of mercury. The abdomen was moderately tender diffusely, and bowel sounds were intermittently active, with no pathological sounds. The remainder of the physical examination was unremarkable. Laboratory data included leukocyte count of 25,700 cells per cu mm on admission, with 82 percent polymorphonuclear cells, 7 percent banded forms, 6 percent lymphocytes, 3 percent monocytes, and 2 percent eosinophiles. Serum sodium was 139, carbon dioxide 27, potassium 3.9, and chloride 105 mEq per liter. Serum urea nitrogen, hemoglobin content, and results of urinalysis, examination of the chest and an electrocardiogram were within normal limits. Two stools were negative for occult blood. An abdominal x-ray film showed diminished bowel gas. On sigmoidoscopy 18 hours after the onset of symptoms the lumen could be viewed only to a distance of 15 mm but in that portion there were no abnormalities. Stool cultures on admission and 18 hours later, as well as culture of a sigmoid colon swab, were positive in heavy growth for V. parahaemolyticus on thiosulfate-citrate-bile salts-sucrose (TCBS) agar[8] but negative for enteric pathogens on routine media. The isolate was confirmed at the California Microbial Diseases Laboratory, and it was found to be type 04:K12, Kanagawa-positive at the Center for Disease Control, Atlanta. On Kirby-Bauer antibiotic susceptibility testing,[9] the tetracycline disc produced a zone of inhibition measuring 22 mm in diameter. Growth on Mueller-Hinton agar was poor.

From the Department of Medicine, Stanford University Hospital, Stanford, and the Infectious Disease Section, California State Department of Health, Berkeley.

Submitted October 26, 1973.

Reprint requests to S. B. Werner, MD, Infectious Disease Section, California State Department of Health, 2151 Berkeley Way, Berkeley, CA 94704.

The patient was treated with intravenous fluids and perchlorpromazine but no antibiotics. Nausea and vomiting ceased within several hours of admission. Diarrhea diminished in frequency and severity, and she was discharged two days after admission. She remained afebrile throughout the illness.

She returned February 26 with recurrence of diarrhea, lower abdominal pain and vomiting. The physical examination was unremarkable except for right lower quadrant tenderness on deep palpation. Leukocytes numbered 29,100 per cu mm with 64 percent polymorphonuclear cells, 26 percent banded forms, 2 percent lymphocytes and 8 percent monocytes. Serum electrolytes, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase and glutamic transaminase were within normal limits. A rectal swab yielded V. parahaemolyticus in small numbers. Tetracycline was given by mouth, 500 mg four times a day (for seven days), and the symptoms resolved two days later.

The patient's husband and two of her children also had eaten small portions of conch on February 19. One of the daughters had diarrhea on February 25. Cultures of rectal swabs from this daughter and the husband on February 26 were negative for enteric pathogens on routine media and TCBS agar. A specimen of the implicated conch which had been refrigerated for only three days was negative for V. parahaemolyticus on March 6.

Discussion

Vibrio parahaemolyticus is an enteropathogenic, facultatively anaerobic, Gram-negative rod which prefers alkaline conditions and a salt concentration of 2 to 4 percent. Unless this organism is specifically sought, it may not be discovered on routine culture for enteric bacterial pathogens. It grows with more difficulty than V. cholerae on MacConkeys medium. Neither of these organisms grows on Salmonella-Shigella agar or EMB agar. Both grow well on TCBS agar, which has a high salt concentration and is alkaline (pH 8.6). In the present case, TCBS agar was used because of the history of recent consumption of an uncooked seafood product. Many cases of gastroenteritis due to V. parahaemolyticus undoubtedly go unrecognized because of failure to culture stool specimens on appropriate media. Stable dehydrated TCBS agar is commercially available. Bacteriology laboratories may stock it for use when the patient's food history is appropriate. Nonselective media may be used if no TCBS agar is available. Since the clinical symptoms are similar to those of salmonellosis and shigellosis, V. parahaemolyticus must be considered in the differential diagnosis of gastroenteritis,[10] particularly when seafood is identified as the cause of a foodborne outbreak.

The relative importance of enterotoxin and invasion in the pathogenesis of V. parahaemolyticus gastroenteritis has not been established. Isolates from diarrheic stool almost always demonstrate the Kanagawa phenomenon while isolates from the environment usually do not.[11] The heat-stable hemolysin responsible for the Kanagawa phenomenon lyses human erythrocytes (Wagutsuma's agar) but not equine erythrocytes.[12] Cell-free culture filtrates (containing the hemolysin) are reported to have no effect on ligated rabbit ileal loops, while live cell suspensions cause reaction.[11] Yahagi has reported that V. parahaemolyticus penetrates epithelial cells and the lamina propria of the ligated rabbit gut,[13] as do shigellae, also favoring the importance of invasion.

Illness from V. parahaemolyticus is generally of sudden onset. The incubation period is usually about 12 hours, but it may vary, from 2 hours to 48 hours.[5] Illness is generally brief and self-limited; death from this disease has only recently been reported in the United States.[14] Antibiotic therapy of cholera shortens the duration of diarrhea and the excretion of V. cholerae.[15] However, antibiotic therapy of V. parahaemolyticus gastroenteritis is not of proved value. The relationship of tetracycline therapy and the remission of the symptoms in the present case cannot be established. Little can be concluded from the susceptibility test reported here, as disc testing for V. parahaemolyticus has not yet been standardized.

Failure to isolate V. parahaemolyticus from the conch meat was disturbing; this could have resulted from overgrowth of other organisms or die-off of V. parahaemolyticus during the six days between the date of ingestion and the date of culture. Negative results on culture of rectal swab specimens taken from other members of the patient's family may have been the result of the long interval (seven days) between ingestion and culture. Indeed, as with most gastroenteritis, the opportunity for isolating the organism diminishes quite rapidly—an argument for early cultures.

Another possibility is that the family members suffered a coincidental and unrelated illness.

Little information is available on the carrier state of V. parahaemolyticus and its public health significance. There has been no evidence of secondary transmission in any of the 13 United States outbreaks. No long-term carriers were identified in the large outbreaks reported from Maryland.[16] Eight-tenths of 1 percent of healthy food workers and 7 percent of healthy sushi cooks in Japan were found to carry the organism during summer months, but the strains found were Kanagawa-negative.[2] Foodborne outbreaks of V. parahaemolyticus are preventable by appropriate cooking and refrigeration practices, and by avoiding contamination of cooked products by raw ones or surfaces and implements that have had contact with raw fish products. Control of the problem in Japan will be difficult, considering the popularity of raw and partially cooked seafood in the Japanese diet.

The available data on *in vitro* antibiotic susceptibility testing are confusing. Studies of disc tests have either used very high antibiotic contents,[17] failed to report zone sizes,[18] or used nonstandard agar medium.[19] These studies have been interpreted as showing sensitivity to tetracycline.[20] However, 13 strains of V. parahaemolyticus tested by the "gutter plate method" showed complete inhibition to tetracycline at 10 μgm per ml with partial inhibition starting at 5 μgm per ml,[18] and five strains tested by a tube dilution technique showed inhibition by oxytetracycline at 5 μgm per ml but not 2.5 μgm per ml. The break-point for tetracycline sensitivity is generally considered to be $\leq$ 4 μgm per ml.[21] It has been suggested that satisfactory disc testing may be performed with trypticase soy broth and Mueller-Hinton agar, both supplemented with 3 percent sodium chloride.[12]

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LETTERS *to the Editor*

Position on Early and Periodic Screening

To the Editor: Recently, the federal government has mandated a health screening program for the Medicaid-eligible population under age 21. In California, the Brown Bill AB-2068, now Chapter 1069 of the Health and Safety Code, is the new State financed program for child health and disability prevention. It is to provide for early and periodic assessment of child health. Physicians who care for children have the obligation to evaluate possible benefits and perils that may develop through implementation of this legislation.

It is unfair to develop schemes that may be for publicity value or serve to justify programs of questionable validity. Prevention of disease by screening is so appealing a concept that wishful assumptions have been made that the methodology is available to assure success. Legislators and the public seem to accept anything that promises to achieve this goal. The value and limitations of mass screening techniques are little understood, yet mass screening has become the modern mystique—the answer to health problems. Can mass techniques be successful in early detection and prevention of physical and mental disability in children? Some think so. These opinions were never proven before legislation was enacted to start mass screening. Health officials must beware of the dangers of implementing screening programs that may be medically and philosophically unsound.

We recognize that the needs of all children are not being met. Mass screening has been assumed to be better than nothing, or a place to start. Until adequate data are available to confirm or deny that massive unproven screening is of value, it would be prudent to conduct pilot studies on a cross-section of children in this state. Specific innovative programs need to be developed for those without care that are comparable to the best. Where medical care is not available because of maldistribution of physicians, isolation, or with migrant children, incentive programs must be created.

An article about early and periodic screening in The Western Journal of Medicine, March 1974 [McNamara JJ: Early and Periodic Screening—Medi-Screen Program Structure and Standard Setting. West J Med, 120:263-266, Mar 1974] stated:

> "This one-to-one interaction is not the model envisioned in Medi-Screen. . . . Determining health status and detecting abnormalities may lead to diagnosis and treatment and may prevent the progression of illness. However, direct responsibility for the health care of populations, except in limited contexts, does not exist. The problem of evaluation and follow-up after the health data are collected is the major challenge facing a program such as Medi-Screen."

Good communication is essential to getting a proper history. A program planned without interaction or responsibility toward the child can become a dehumanizing experience that will never foster communication. It will encourage the authoritarian approach that says, "I know what you need—don't communicate your feelings—my values must be your values." Communication permits one to pick up the mixed message where the tone and content do not agree. The establishment of rapport in a one-to-one relationship, plus the skill and ability to clarify of the interviewer will determine the quality of the history obtained. In turn, this will best direct the child's care.

A good medical system provides trust, communication and mutual respect. It must be planned so that receivers and providers want to give their cooperation. Screening programs run the great risk that those who do not have a primary source of medical care, such as a hospital plan, a clinic or a personal physician, will be processed in a style that will leave them in the same position—no place for treatment, no funds, no follow-up, and no one person responsible.

Health is based on physical, intellectual, emotional and social factors interlocked in a complex manner. It is a continuum that begins at birth and extends throughout life. Can we assume that if we stop and screen a child at one point on

this continuum, we can prevent and detect disease? Can we expect screening of individual organ systems or the measurement of certain biological parameters to accomplish this? There is no definite knowledge that proposed procedures will be of value to children and there is potential for harm.

Health officials must beware that activism without rationality, even for the noblest ideals, may exploit those with the greatest problems. Funds to meet the needs of children must not be dissipated by the commercial motivation to capitalize on a screening process. On the other hand, funding must be adequate to purchase the required services or a hoax will be perpetrated on these children. Many who are getting inadequate diagnosis and treatment are those who are poor, uneducated, uncared for, unneeded, unwanted and unloved. They have experienced second rate medical evaluation, prevention, and therapy in the past—let us not offer them more of the same.

MARTIN GERSHMAN, MD
San Francisco

Tricuspid Valve Replacement

TO THE EDITOR: I recently read the article entitled "Tricuspid Valve Replacement in Carcinoid Heart Disease," by Dr. Harold G. Lund, Dr. Richard J. Cleveland, Dr. Lowell H. Greenberg, Dr. Maurice Lippmann and Dr. Malin R. Dollinger. This was published in the May, 1974 edition of THE WESTERN JOURNAL OF MEDICINE, Volume 120, Number 5 and appeared on Pages 412-415.

The authors' concluding statement reads: "This appears to be the first reported patient with carcinoid heart disease to have successfully undergone tricuspid valve replacement." An article (of which I was one of the authors) entitled "Carcinoid Heart Disease: Surgery for Tricuspid and Pulmonary Valve Lesions," was published in the August, 1973 edition of *The American Journal of Cardiology,* Volume 32 on Pages 229-233.

Doctor Lund's article stated that their patient was operated upon in June, 1972. Our patient was operated upon on January 28, 1972—four or five months before Doctor Lund's patient was operated upon. Although Doctor Lund's patient died four months following surgery, our patient is living and well as of this date, having just graduated from the University of Nevada at Las Vegas. Since the dates of our operations were fairly close (being only four months apart), I can see how our article may have been missed.

We do not claim being the first to replace the tricuspid valve. In our article we made note of the fact that in 1966 Dr. J. M. Aroesty had described a patient's having been successfully operated upon for carcinoid heart disease. We corresponded with Doctor Aroesty, and he stated his patient did well until October, 1971, when he died of increasing hepatic failure.

Doctor Lund et al obviously had not reviewed the literature sufficiently to determine the fact that Doctor Aroesty was the first to successfully replace the tricuspid valve for carcinoid disease. I believe we were second, and Doctor Lund et al were third.

JEROME HAROLD KAY, MD
Los Angeles

EDITOR'S NOTE: For this journal's part in the record, let it be noted that the article by Lund and coworkers was first submitted for publication in May, 1973, and was returned to him with suggestions for revision. Hence, as Dr. Kay correctly surmised, they had no way of knowing, from a survey of the literature and then current indexes, of the paper by Kay and coworkers which appeared in August, 1973.

Trauma Rounds

Chief Discussant
EDWIN J. WYLIE, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Wylie EJ: Management of ruptured aneurysms of the abdominal aorta (Trauma Rounds). West J Med 121: 71-76, Jul 1974

Management of Ruptured Aneurysms of the Abdominal Aorta

FRAZIER HUBBARD:* The patient is a 70-year-old white man who was admitted to the emergency room of a major hospital on January 6, 1974, with chief complaint of steady cramping pain in the left lower quadrant of the abdomen. On examination he appeared to be relatively normal, with no specific abdominal findings. Blood cell count and urinalysis were within normal limits. The patient was given analgesia and sent home to return if the pain persisted.

Next day he returned with exacerbation of the pain. During routine examination he became hypotensive and temporarily unresponsive. Intravenous lines were placed and a pulsating abdominal mass was felt. The patient was taken immediately to the operating room and it was found that an abdominal aortic aneurysm had ruptured. Besides a liter of free blood in the peritoneal cavity there was a large retroperitoneal hematoma. The suprarenal aorta was cross-clamped to facilitate control of the bleeding and a dacron aortoiliac bifurcation replacement graft was inserted. The patient required 12 units of whole blood during the procedure.

In the postoperative period the blood pressure was normal but the urinary output progressively fell and the blood creatinine rose despite the administration of fluids, mannitol and furosemide (Lasix®). The patient was transferred to San Francisco General Hospital for renal dialysis, presumed necessary because of ischemic renal damage from shock and aortic cross-clamping.

BARRY GARDINER, M.D.:† We are fortunate to have, as our guest discussant today, Dr. Edwin J. Wylie, professor of surgery and chief of vascular surgery at the University of California School of Medicine. Dr. Wylie, will you comment on the manifestations of the ruptured aneurysm and describe what you consider the key factors in diagnosis?

EDWIN J. WYLIE, MD:‡ The nature of the presentation of the ruptured aneurysm determines the appropriate reaction. There are a number of different initial manifestations, including three rare types of rupture. The three unusual manifestations consist of: (1) rupture into the adjacent vena cava with formation of an arterial-venous fistula, (2) rupture into the duodenum with massive gastrointestinal hemorrhage, and (3) dissection into a plane behind the psoas muscle with back pain and the presentation of an inguinal mass which may be confused with a strangulated hernia.

Rupture into the vena cava is an extremely rare phenomenon. It is described in the literature,

*Senior Medical Student, Trauma Service.

Sponsored in part by NIH grant GM 18470 and the Northern California Trauma Committee, American College of Surgeons.

Reprint requests to: D. D. Trunkey, MD, University of California Service, San Francisco General Hospital, San Francisco, CA 94110.

†Chief Resident, Trauma Service.

‡Professor of Surgery and Chief of Vascular Surgery, University of California, San Francisco, School of Medicine.

but I myself have only seen two such cases. The patient with rupture into the vena cava goes into acute cardiac failure and presents with a high venous pressure and acute respiratory distress. He usually arrives by ambulance, with everybody cognizant of the cardiac nature of the emergency. The key to diagnosis is the presence of a palpable, pulsatile mass and a loud "machinery" bruit on auscultation. Treatment requires immediate exploration and control of the aneurysm. All the medical therapy in the world will not control the cardiac failure.

The manifestation of duodenal rupture consists of massive gastrointestinal hemorrhage which may present as hematemesis or melena. This is also a rare complication of a primary aneurysm. The diagnosis can be made only at operation, but it can be suspected if a patient with a massive gastrointestinal hemorrhage has a pulsatile mass palpable in the epigastrium. The catastrophic nature of the hemorrhage usually dictates immediate operation.

The third type consists of a small aortic blister rupturing posteriorly and dissecting paravertebrally along the psoas plane. It often presents as a mass at the inguinal ligament, which may be tender. The abdominal pain may be mild to moderate, not as severe as it was in the patient we are discussing here. The patient is usually apprehensive. On physical examination, the psoas sign is present, a leg is flexed and the patient very reluctant to extend it.

The most common rupture is of the type seen in the present case. The standard manifestation consists of sudden abdominal pain, often associated with back pain. The rupture can be in the wall of the aorta itself, or it may be in adjacent tissue around the aorta, or into the retroperitoneal area or into the free peritoneal cavity (Figure 1). The first three routes of rupture ordinarily follow one another in order, and the first manifestation is usually a sudden drop in blood pressure. Tissue pressure builds up and contains the rupture as the systemic pressure falls concomitantly. The patient may have an initial episode of faintness from loss of blood, sometimes just several hundred milliliters. Then the pain subsides, the vital signs return and the patient feels better. This is a perilous trap, for there then may be a secondary rupture into the free peritoneal cavity with death following immediately. Operation, therefore, is not a matter to be delayed. Any patient with suspected impending rupture should be operated upon as soon as the abdomen can be prepared and anesthesia induced. Taken together acute abdominal pain and a pulsatile mass are indication for immediate laparotomy.

The other criterion for operation is the presence of shock. For all practical purposes, shock and the presence of a palpating, pulsating epigastric mass mean rupturing aneurysm until proven otherwise. Generally speaking, patients with rupturing aneurysms can be divided into two types, those with and those without shock. The course of the two is entirely different. The mortality rate for those arriving in shock is 75 percent; for those arriving not in shock, 25 percent. The overall mortality rate is about 50 percent. This is the national average and is essentially everybody's experience.

One should not wait until blood is cross-matched. Type-specific blood should be sent for and held in the operating room. If the patient's condition suddenly deteriorates, the blood can be given. Since many of these patients are intensely vasoconstricted, one must be on the look-out for a precipitous fall in blood pressure as the induction of anesthesia releases the constriction. If the patient's condition deteriorates during induction, don't wait for full anesthesia and don't wait for

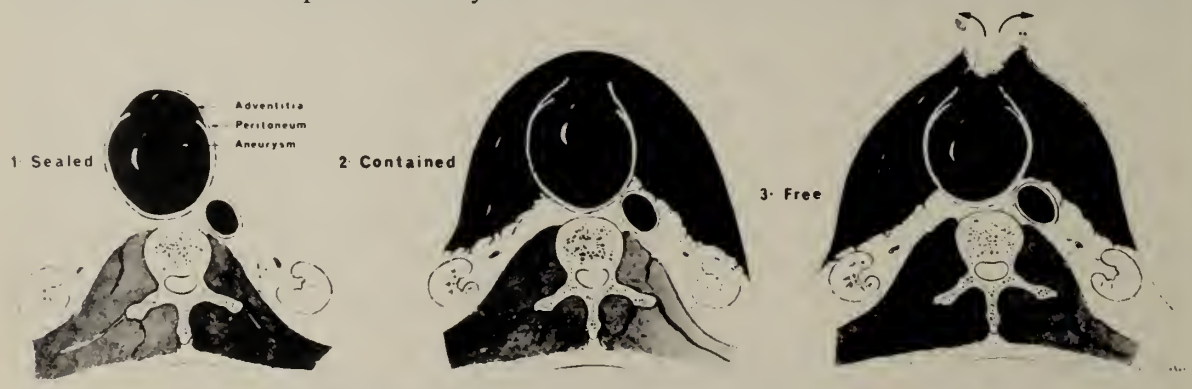

Figure 1.—Types of abdominal aortic aneurysm rupture

the razor to shave the abdomen. Proceed immediately with the incision and obtain control. The most important thing you can do for the patient is to stop the source of bleeding and save the transfused blood until you have control of the bleeding point.

Occasionally, the patient has an inflammatory aneurysm. The pathogenesis of this lesion is not known, but the wall of the artery is edematous, almost cartilaginous in nature, and is very thick. The lesion may be associated with sudden, severe abdominal pain, but rarely is it associated with acute rupture. Even so, since inflammatory aneurysms cannot be diagnosed in advance, it is better to err on the side of immediate operation rather than to defer operation and overlook the possibility of free rupture.

DR. GARDINER: *Dr. Wylie, how do you obtain control of the aorta when you open such an abdomen?*

DR. WYLIE: This is the critical part. When the abdomen is opened and there is a bulging, retroperitoneal hematoma with no free blood inside the abdomen and the blood pressure is stabilized at the head of the table, the dissection should be initiated distally and control of the iliac vessels obtained. This permits complete control to be developed rapidly once the proximal dissection is started and the aneurysm entered. All the anatomic details have been set out and the least blood loss will develop, as there will be no back bleeding with the distal control obtained, and the graft can be put in place much more rapidly with the distal dissection already done.

Repair of the inferior mesenteric artery should be deferred until it can be reached inside the aneurysm. In these large aneurysms with a periaortic hematoma, the only place you can get ready access to the inferior mesenteric artery from outside of the lesion is far distal on the artery, and that might compromise collateral flow. For this reason, it is better to wait until the aneurysmal sac is opened and the vessel can be controlled from within.

If the patient is in shock when the abdomen is opened or there is free intraperitoneal bleeding, you must first go for the proximal portion of the aorta. The hematoma often will have done much of the dissection for you, as it will encircle the upper aorta and displace the other anatomical structure away from the aorta. If you go into the hematoma and reach directly for the neck of the aneurysm, you can usually pass your two fingers down on each side of the aorta and apply the crossclamps. The aorta does not need to be mobilized completely proximally as would be done in an elective procedure. There is one big point of risk, and that is the renal vein which runs across the upper end of the neck of the aorta. I have seen cases in which more blood is lost during aneurysmectomy from damage to this vessel than from anything else. If the renal vein is in the way or is inadvertently torn, I would have no reluctance to clamp it and ligate it. Collateral flow from the left renal vein is adequate to preserve the kidney. This facilitates dissection and may be of value even in elective aneurysmal operations.

If for some reason it is not possible to get at the neck of the aneurysm and the patient is bleeding, the best alternative is to open the proximal portion of the aneurysm immediately and put your thumb in the proximal aorta. Ordinarily, the neck of an aneurysm fits snugly around the base of the interphalangeal joint and good control can be obtained. The neck of the aneurysm can then be mobilized. If this becomes difficult, I consider using something like a Foley catheter, which can be inserted up alongside the thumb and into the upper abdominal aorta. Inflating the balloon then controls the bleeding. An assistant has to hold the balloon to keep it from being displaced downward, but anastomosis of the graft of the aorta can be carried out with the balloon in place. The catheter, of course, should be passed through the graft before it is inserted into the aorta.

Another alternative is to expose the aorta at the level of the celiac axis by coming down through the gastrohepatic ligament to expose the aorta just as it comes through the diaphragm. A vascular clamp placed here is effective in occluding the circulation. Apparently that was done in this case herein described. I have not seen any problems with ischemia because of interruption of blood supply to the cord, and I would not hesitate to clamp the aorta here as long as necessary.

Another way to control the aorta—I haven't had occasion to use this for a long time—is to prop the patient in a partial lateral position with sandbags and open the left side of chest and crossclamp the descending thoracic aorta. In old patients with aneurysms, this adds another insult and should be avoided if possible.

A PHYSICIAN: *Do you have any arbitrary rule about the length of time you can crossclamp the suprarenal aorta?*

DR. WYLIE: I believe you can crossclamp the aorta for thirty or forty minutes, and perhaps even longer than that if there is underlying renal vascular stenosis. One of the problems is that the pre-existing shock may produce damage, and I believe that the suprarenal crossclamp alone was not the factor responsible for renal failure in the present case. One of the other problems that produces renal failure is that the very process that produces degeneration of the aorta produces degenerative atheromatous material in the aorta above the renal arteries. Compression of the artery may fragment this atheromatous material, which then can become emboli in the renal arteries. I believe that this factor was responsible for renal failure in at least two cases that I have seen.

A PHYSICIAN: *Does clamping the infrarenal aorta have any effect on the kidney?*

DR. WYLIE: Dr. Sam Powers, many years ago, after collecting information from all the community hospitals in the Albany area, wrote a paper saying that clamping the infrarenal aorta could cause renal failure. I believe a more significant factor is "declamping shock." The release of the occluding clamp after placement of the graft results in a period of hypotension which further aggravates shock. Certainly, if at the time of release of the occluding clamp the patient is behind in blood replacement, the hypotension can be profound and prolonged. For this reason, every effort should be made to restore the blood volume to normal or above normal just before release of the clamp. Another way is to release the clamp slowly. The clamp can be taken off and the graft compressed digitally, and then you can open up the circulation to one leg at a time or one hypergastric artery and then one external iliac at a time over a period of ten or fifteen minutes.

A PHYSICIAN: *What type of graft do you use, and does your technique vary between elective and emergency cases?*

DR. WYLIE: The only variation of my technique is the upper anastomosis. I always use a knitted, dacron graft. Usually in emergency I do not transsect the aorta completely or mobilize it completely and the aneurysm is in continuity with the proximal aorta. Usually in the case of ruptured aneurysm, I only cut across the arteries two-thirds of the circumference of the aorta proximal to the aneurysm. I then cut the posterior intima circumferentially and use this groove as a guideline for the posterior suture line which is developed within the aorta.

A PHYSICIAN: *How do you cover the graft after completion of placement and restoration of flow?*

DR. WYLIE: I practically never take the aneurysm out. I strip out the lining of the aneurysm and use the remaining portion of the wall to close over the dacron graft. At this point of stripping, the lumbar arteries and the middle sacral artery have to be oversewn. The orifice of the inferior mesenteric artery is oversewn at the same time from within the aorta. I cut off all but 4 to 5 centimeters of the aortic portion of the graft so that bifurcation comes just below the site of anastomosis. It is then possible to take the left hand wall of the aneurysm and suture this between the two legs of the graft, and the right wall of the aneurysm is overlapped across the right limb of the graft and over the left side of the graft. If this is sutured down tightly, good hemostasis is obtained and the graft is prevented from coming in intimate contact with the duodenum.

One of the common complications of operations of this type is postoperative bleeding, so I spend considerable time tidying up the retroperitoneum and making sure of hemostasis. This cuts this complication to a very low level.

DR. GARDINER: *Are there any other complications that we should consider in the management of these patients or in aneurysmal operations?*

DR. WYLIE: Renal failure is the complication that is unique to operation on a ruptured aneurysm. Cardiac failure can, of course, occur after an episode of shock and blood loss. Many of the patients have cardiac disease and may not be in optimal condition for such operations. They can have an acute myocardial infarct as a complication of the operation. I have not been particularly aware of thrombotic complications although many studies have been done which suggest that the blood of these patients is hypercoaguable. Complications of distal arterial thrombosis are relatively rare and in my experience so are thromboembolic pulmonary complications. I think it is very im-

portant to administer heparin to these patients. I give them 3,500 units of heparin before crossclamping the aorta, then an additional 2,000 units every half hour during crossclamping, although usually only one dose of heparin is indicated.

A PHYSICIAN: *Do you reverse the heparin with protamine?*

DR. WYLIE: That usually isn't necessary. I prefer to let the heparin wear off. When it is given in the dosage that I just prescribed, complications of heparin therapy are rare.

Another complication to be considered—though it is rarely seen after operations for aneurysm—is "trash foot." Usually it is associated with operations carried out for occlusive diseases. In repair of aneurysms, gelatinous clot in the sac may break off in large chunks, but the substance is relatively sticky and does not cause anywhere near the same embolic problem as seen in patients with occlusive disorders. To avoid this complication it is important to backfeed the iliac arteries before restoration of flow. When the aorta is particularly dilated and filled with lots of grumous material, careful attention should be given to removing it lest it cause peripheral embolization.

A PHYSICIAN: *Do you want to comment on ischemic damage to the colon?*

DR. WYLIE: Recognition of ischemic colitis may be very difficult. The initial damage is to the mucosa, and the outward appearance of the colon may be relatively good. The colon should be carefully examined and the pulses in the superior mesenteric artery palpated before the abdomen is closed. The patient is at greatest risk of ischemia of the colon in the presence of occlusive disease of the superior mesenteric artery or with hypogastric artery disease or in circumstances in which the hypogastric artery has not been revascularized at the time of aneurysm resection because of aneurysm degeneration. When aneurysms extend down into the common iliacs, we preserve the inferior mesenteric artery until the operation is completed. If we have not been able to revascularize at least one hypogastric artery and if there is any question about the adequacy of the collateral from the superior mesenteric artery, then the inferior mesenteric artery can be reimplanted in the graft. Rarely is this necessary, however; compromise of collateral circulation should not occur, provided the critical collateral vessel is not destroyed by ligating the inferior mesenteric artery away from the wall of the aneurysm. If bloody mucus is passed by rectum in the postoperative period, ischemic damage to the colon must be considered. A further clue, on proctoscopic examination, is greyness of the mucosa. If there is any question, operation should be done and if the colon is at all ischemic to external appearance, large bowel resection and colostomy should be carried out.

FRANK LEWIS, MD:* *As a way of preventing this complication of rupture, could you give your criteria for operation on the "elective" aneurysm? If the aneurysm is asymptomatic, at what size do you think the hazard of rupture is sufficient to warrant operation?*

DR. WYLIE: In our series we have only had two cases of rupture of aneurysms smaller than 6 centimeters in diameter. For this reason, then, I believe that the arbitrary 6-centimeter rule is appropriate. Any asymptomatic aneurysm of less than 6 centimeters can probably be observed until it enlarges beyond that size or symptoms appear. However, if the patient is young and in good health, we might consider operation if the lesion is only 5 or 5.5 centimeters in diameter. Once the aneurysm exceeds 6 centimeters, if the patient's condition is optimal and life expectancy reasonably good, corrective operation can be carried out with expectation of less than 2 percent mortality.

F. WILLIAM BLAISDELL, MD:† We can summarize this presentation by stating that the risk of aneurysm operation in elective cases is 2 percent, but when the lesion ruptures it is 50 percent. When an aneurysm exceeds 6 centimeters, most vascular surgeons would advise elective resection.

Ruptured aneurysm can present in a number of different ways—rupture into the adjacent vena cava with immediate profound cardiac failure, rupture into the duodenum with massive gastrointestinal hemorrhage, and rupture into the psoas plane causing a mass in the groin. The typical manifestation, however, is abdominal and back pain often accompanied by transient shock due to rupture into the retroperitoneum which, if un-

*Attending Staff.

†Chief of Surgical Service, San Francisco General Hospital, and Professor of Surgery, University of California, San Francisco, School of Medicine.

treated, is followed by a free rupture into the peritoneal cavity. When a patient presents with acute pain and a palpable mass, impending rupture should be assumed and the patient should be taken to the operating room without delay. If shock is present immediate operation is mandatory. The anesthesiologist should not wait for the presence of crossmatched blood. Control of the aorta can be obtained by going into the plane of periaortic blood dissection at the proximal end of the aneurysm if free hemorrhage is occurring, or simply by entering the aneurysm and putting a thumb into the aorta. If the neck of the aneurysm is so dilated that insertion of a thumb will not control bleeding, a Foley catheter can be used. Occasionally, crossclamping of the aorta at the level of the diaphragm is of value, and rarely it may be necessary to open the left side of the chest to obtain control by clamping the descending thoracic aorta.

If the patient's condition is stabilized and he is not in shock at the time of laparotomy and no free bleeding is occurring, it is appropriate to obtain distal control before the hematoma is breached to obtain proximal control. A standard, knitted, dacron graft is used to replace the damaged section of aorta. Declamping shock should be avoided by careful, slow release of the circulation after the graft is in place, and the graft should be carefully wrapped with the residual wall of the aneurysm.

Complications of operation for ruptured aneurysm include renal failure, myocardial failure, ischemic damage to the colon and, rarely, peripheral embolism of atherosclerotic fragments or portions of a clot from the aneurysm.

Removing a Troublesome Contact Lens

How to avoid getting up at 2 o'clock in the morning and going out to make a housecall on some patient to get a contact lens out?

It happened to me not too long ago . . . and of course, it was a doctor's daughter who had worn her contacts 15 hours that day and had only a tolerance of 11 or 12 hours. It was 2 a.m. I could hear her on the phone. She was about 17 or 18, but she was really carrying on . . . and the pharmacies don't deliver at that hour. I told this doctor to phone the pharmacy and have a taxicab bring out some Pontocaine® ointment. He said, "Oh, I can't get that in her eye." And I told him how to rub it on with his finger on the lashes and gently work it in until they could get the eye open . . . and then, when the ointment took hold and they could get the eye open, that he certainly could get the lens out with her little suction cup. Or, if he couldn't do that, at least he could take an eye cup and some warm water . . . and wash it out. This succeeded. I saw her the next morning and her comment was, "I never believed that I would be able to get to your office this morning!"

—George E. Morgan, MD, *Los Angeles*

Extracted from *Audio-Digest Ophthalmology*, Vol. 12, No. 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Bristow LR: The myth of sickle cell trait (Medical Opinion). West J Med 121:77-82, Jul 1974

The Myth of Sickle Cell Trait

LONNIE R. BRISTOW, MD, *San Pablo, California*

Recently emphasis in the problem of sickle hemoglobinopathy has been on mass screening of the black population. Concern about the alleged danger in having sickle cell trait itself is offered as part of the justification. This danger is disputed and a position developed for the benign status of sickle cell trait and the potentially serious social harm to blacks so identified. Programs are suggested to foster improved medical care availability and early detection for those with sickle cell anemia. It is suggested that mandatory patient programs be avoided, and that research receive greater emphasis.

SINCE EARLY 1971 screening blacks for the purpose of identifying persons possessing the gene for sickle hemoglobin has been a subject of great interest. Often, the impetus for this movement came from lay persons motivated by a genuine desire to serve the community. They were joined by many professional and governmental organizations equally well motivated. Lay publications, such as Reader's Digest,[1] speak of "identifying sickle cell carriers and thus preventing the disease through genetic counseling."

The clinics indicate counseling as their major program of remedy for the persons identified as having heterozygous or homozygous hemoglobin-S. The premise of prevention is advanced although the only way to prevent sickle cell anemia is for those who possess the hemoglobin-S gene either to avoid reproduction altogether or to predetermine the genetic pattern of any potential mate. It is contended that the person with sickle cell trait is much sicker than was previously realized and therefore also needs guidance for this compromised state of health.

It is largely the hypothesis of a compromised state of health in the person with sickle cell trait that justifies the existence of programs of mass screening. This eventually resulted in the National Sickle Cell Anemia Control Act being passed by Congress in the spring of 1972. The act[2] clearly states that "efforts to prevent sickle cell anemia must be directed toward increased research . . . and the education, screening and counseling of carriers of the sickle cell trait." It allowed for up to twenty-five million dollars to be spent in 1973 on research and voluntary screening and counseling programs. This figure can be increased to fifty million in 1975. However, between 70 and 80 percent of funds are earmarked for mass screening and genetic counseling, with only 20 to 30 percent going to research and therapy. It is the purpose of this paper to examine the evidence relating to the heterozygous state of hemoglobin-S and to show that its negative effects on health have been exaggerated.

The author is a member of the Sickle Cell Advisory Committee, Contra Costa County Health Department, Martinez, California.

Submitted January 25, 1974.

Reprint requests to: L. R. Bristow, MD, 2023 Vale Road, Suite 202, San Pablo, CA 94806.

Background

The homozygous-S state, henceforth to be called sickle cell anemia, is present when both hemoglobin genes are of the S variety. A single S gene, when combined with an A gene, constitutes what has been termed the A-S state, henceforth to be called sickle cell trait. In both the anemia state and the trait state, blood has the property of sickling when it has been subjected to sufficient deoxygenation (as in the so-called sickle cell preparation). Sickle cell trait can best be distinguished from sickle cell anemia or combinations of heterozygous-S with other non-A hemoglobin genes by electrophoretic techniques. The sickling phenomenon in this country is seen mainly in persons of African ancestry, but it has also been demonstrated in significant, although lesser, frequency among Sicilians, Arabs, some tribes of American Indians, and in some areas of Greece and Mexico. Screening programs that confine their efforts to blacks will therefore overlook a persistent reservoir of the gene.

It is well established that the incidence of sickle cell anemia among black Americans is approximately one in five hundred, and that between 7 and 10 percent of black Americans have the sickle cell trait. There are other heterozygous-S combinations which have definite pathologic importance but their combined incidence is much less than 1 percent of black Americans.[3]

The Ubiquitous Sickle Cell Trait

The sickle cell trait has been said to cause a variety of vascular thrombotic phenomena such as priapism, infarcts of pulmonary, splenic and cerebral vessels[4] and the "sudden death syndrome."[5]

All of these are presumably mediated through dehydration, acidosis and anoxia, singly or in combination. Each of these clinical problems has had excellent documentation of association with sickle cell anemia. Since sickle cell trait has *in vitro* sickling in common with sickle cell anemia, it seemed logical to expect that enough dehydration, acidosis or anoxia in a person with trait ought also to produce *in vivo* sickling with similar clinical catastrophes. There is some support for that supposition in that autopsy examination of every cadaver with sickle cell trait does reveal the presence of intravascular sickling.[6,7] However, this finding is due to the postmortem development of acidosis and anoxia that occurs regardless of the initiating cause of death. This phenomenon may be part of the basis for the exaggeration of the consequences of sickle cell trait. There is reason to doubt that living man, with his homeostatic mechanisms functioning even poorly, is capable of reaching such desperate levels of imbalance as to lead to *in vivo* sickling in a person with sickle cell trait. This will be touched upon later.

Sickle cell trait does occasionally produce hyposthenuria and hematuria.[8] Hyposthenuria creates no direct medical problems itself but is of academic interest. Hematuria appears in no more than 1 percent of people with sickle cell trait and although it rarely poses a life-threatening problem it can sometimes be a problem in differential diagnosis. Pregnancy in women with sickle cell trait has twice the likelihood of pyelonephritis that it has in pregnant women with normal hemoglobin,[3,9] but there is no difference from normal persons in response to treatment. These two problems were mentioned first because they have excellent documentation in the form of large group case studies. Of great importance is the fact that there is no evidence relating their occurrence to altitude or other environmental hypoxia (such as swimming or anesthesia).

Priapism

Problems believed to be associated with sickle cell trait are often anecdotal, meaning they are reported in series so small that all conclusions are necessarily weakened. Priapism has had a well-documented association with sickle cell anemia, and the onset is usually in the pre-pubertal male. Recently an association with sickle cell trait has been claimed.[10] Priapism has also long been known to occur idiopathically. Grace's series[11] had 11 idiopathic cases with an average age at onset of 40 years. Farrer's series[12] had 11 idiopathic cases with an average age at onset of 43 years. It is interesting that the three case reports[10-12] in which the condition is ascribed to sickle cell trait gave the age at onset as 34, 37 and 39 years—strikingly similar to the onset of the idiopathic variety.

Oral Contraceptives

In 1970 an article[13] reported a case of a 20-year-old black woman with sickle cell trait who had a history of two years' use of oral contraceptives and a vertebro-basilar artery insufficiency syndrome. It was suggested the oral contraceptive

may have lowered oxygen tension sufficiently to have induced sickling. No evidence was offered as to how oral contraceptives could reduce oxygen tension in any direct manner. Nevertheless, this article has been the basis for the recently advanced proposal to withhold prescriptions of oral contraceptives from women with sickle cell trait.

Several population studies[14,15] have shown the risk of thrombo-embolism in general is eight times greater among all women taking the pill, and the risk of cerebro-vascular disease in particular is six times greater than in women who are not taking the pill. For some unexplained reason young women who experience clinical stroke while taking oral contraceptives show at least a 25 percent incidence of involvement of the vertebro-basilar area of the brain.[16,17] This area of the brain is involved only rarely in young persons with stroke who have not been taking oral contraceptives. This would seem to offer a different interpretation to the previously mentioned 1970 case report[13] of the 20-year-old black woman who did indeed have a vertebro-basilar artery insufficiency syndrome.

General Anesthesia

General anesthesia for persons with sickle cell trait has been another matter of concern. The hypothesis is that such persons have a lowered tolerance of the anticipated hypoxia and possible acidosis associated with general anesthesia and the post-anesthetic state.[18,19] There are some group studies available on the question. In 1969 a report from Kings County Hospital Center in New York[20] reviewed 47 sickle cell trait patients who had received 55 general anesthetics between 1956 and 1957. All patients had "smooth uncomplicated" hospital courses. In 1971 Oduntan and Isaacs[21] reported experience with general anesthesia in 18 patients with sickle cell trait. There were no complications during anesthesia or in the postoperative period, although there were two later deaths. One occurred suddenly (presumably from a pulmonary embolus) 14 days after operation and the other, 15 days after operation, was caused by metastatic cancer found at operation. In neither instance was there evidence to link the combination of sickle cell trait and general anesthesia with the death two weeks later.

Sudden Death Syndrome

A connection with the "sudden death syndrome" was suggested by Jones, Binder, and Donowho.[5] They reported upon four black soldiers whose deaths they attributed to sickle cell trait. The deaths occurred during a 12-month interval at an Army basic combat training post which was situated at an altitude of 4,060 feet. During that time approximately 4,000 black soldiers underwent training in that facility. Four died suddenly, within 25 hours of becoming ill. All were black, had been exercising at this altitude, had the sickling phenomenon observed in their vasculature at postmortem and shared the mystery of having no other diagnosis. Of interest are several other points. One of the trainees lost consciousness while in the middle of running only once around his barracks and another soldier died within moments of his exercise which consisted simply of a 20-yard crawl. The 4,060-foot elevation of the Army post is not unduly high compared with many other points in this nation where black people live. The findings at postmortem of sickling throughout the vascular systems of the four soldiers has been explained earlier. The autopsy findings demonstrated no old infarcts that might have suggested previous sickling difficulties. Two of the recruits died of disseminated intravascular coagulation, yet there was no mention that any bacteriologic cultures had been obtained. A third recruit was found at postmortem to have "marked coronary arteriosclerosis." Previous studies by Kuller and others[22] have shown that arteriosclerotic heart disease accounts for approximately 22 percent of all sudden, unexpected deaths in the 20-to-39-year age group, so that in this case there was an appropriate explanation without invoking sickle cell trait. The fourth recruit was anemic but hemoglobin electrophoresis had not been done, making it distinctly possible that he may have had a combination of hemoglobin-S with some other abnormal type of hemoglobin. These same objections have been pointed out by others.[23]

A prospective study was done later on the same Army post by some of the original investigators.[24] Three months after the last of the four mysterious deaths, Binder and Jones identified 73 cases of sickle cell trait in the next 1,000 black recruits. These men were closely observed throughout their basic training (training that was identical to that given to the four men who had died "suddenly" during the preceding year). No morbidity and no deaths were observed. This article stressed that most persons with sickle cell trait were usually unaware of their abnormality.

Population Studies

There are epidemiologic approaches which can be used to determine if the mere possession of sickle cell trait itself is a threat to life. Three examples are as follows:

First, if a factor such as sickle cell trait is associated with a significant mortality, there should be an apparent difference in its frequency between those who die and those who continue to live over a given time span. In 1961 McCormick[6] reported a survey for hemoglobin-S in the blood, at autopsy, of 1,248 black patients over the age of one month. These autopsies were performed during a 31-month period in three large hospitals in Tennessee. McCormick found sickle cell trait in 120 cases (9.6 percent). He also collected blood specimens from 1,660 living black patients in the same hospitals. The second group of specimens, from people who survived whatever had brought them to the hospital, served as controls against the autopsy group. In the group of 1,660 living patients, 140 (8.5 percent) had sickle cell trait. The difference between the two groups has no statistical significance.

Second, if sickle cell trait were contributing to death the average age at death of the affected persons should be lower than for those not affected. The 1,104 black patients in whom autopsy revealed normal (A-A) hemoglobin had an average age at death[6] of 47.4 years. This is remarkable for its similarity to the average age at death in the sickle cell trait group (47.3 years).

Third and last, one can examine the incidence of a suspect condition in progressive age groupings. For example, if left-handedness were somehow a lethal handicap one should see progressively fewer left-handed people in older age groups. In 1970, Petrakis[25] and others looked for sickle cell trait in more than 4,000 black persons in an urban area in Northern California. The findings were grouped by ages of from 5 to 20, 21 to 49 and 50 years and over. The overall incidence of sickle cell trait was 8.7 percent and there was no statistically significant "change in frequency of sickle trait with advancing age."

High Altitude Flying

Much of the initial impetus for concluding sickle cell trait is dangerous came in some articles after World War II which sought to link sickle cell trait with splenic infarction during flight. In 1947 Sullivan[26] reported an 18-year-old man in whom a probable splenic infarct developed while he was flying across the Rocky Mountains. Two months after subjective recovery the soldier's spleen was still palpable, though no longer tender. This soldier was also known to have significant target cell formation on peripheral blood smear. One would now consider this a likely case of either S-C or S-thalassemia disease rather than sickle cell trait as was originally concluded. Since electrophoresis was not available then, these possibilities could not have been explored.

During the next few years a number of observers reported[27-30] isolated additional cases as they occurred. Hemoglobin electrophoresis and alkali-denaturation were added to the diagnostic armamentarium during that period. If the papers written by Conn,[27] Cooley et al,[28] Rotter et al,[29] and Smith and Conley[30] during the mid-1950's are read carefully, they compile the cases of 23 different persons with splenic infarction occurring during aerial flight. Twenty-one were examined by hemoglobin electrophoresis, and only four had alkali denaturation studies. Fourteen patients showed A-S hemoglobin patterns; eight of the 14 had either negative or highly questionable sickle cell preparations. This latter finding raises the distinct possibility that these persons with negative sickle cell preparations and "positive" electrophoretic patterns may have had hemoglobin-D trait rather than sickle cell trait. Hemoglobin-D and its properties (identical electrophoretic mobility with hemoglobin-S but no solubility change with deoxygenation)[31] were not recognized at the time of those investigations and consequently could not have been considered. Of the 21 patients studied with electrophoresis, six had S-C disease, one had S-thalassemia and there is a very strong possibility that many of the remaining 14 either had S-thalassemia or combinations of hemoglobin-D trait.

A hematologic survey[3] of 3,500 black women in a Washington, D.C., prenatal clinic indicated the A-S state was 16 times more frequent than A-D, which in turn was almost five times more frequent than S-C disease in that study group.

In 1945 an Air Corps study[32] of black aviation cadets who were in various stages of training for both fighter and bomber groups was done at the Tuskegee Army Air Base. A group of black combat veteran pilots was also studied. The incidence of sickle cell trait was determined in each group and in the cadets who were eliminated from training. This study showed the incidence of sickle

cell trait at every stage of training (and in the combat veterans) stayed in the narrow range between 7.1 percent and 7.7 percent. The incidence of sickle cell trait among the cadets eliminated ranged between 4.4 percent in the primary trainees who "washed out" and zero in the more advanced trainees who failed. Such figures show the sickle cell trait trainees were at no discernible disadvantage.

More recent investigations[33] show that other hemoglobins have an interaction with hemoglobin-S when they are combined in a heterozygous molecule. This interaction influences the ability of a cell to sickle during deoxygenation. In ascending order of strength when combined with hemoglobin-S, hemoglobin A, C, and D are known to promote sickling during deoxygenation. Phrased another way, cells of hemoglobin A-S blood only begin to sickle at oxygen tensions of approximately 15 mm of mercury[34] while cells of hemoglobin S-C blood will begin to sickle at 30 mm of mercury. Cells with hemoglobin S-D will begin to sickle at oxygen tensions which approximate those noted for hemoglobin S-S (60 mm of mercury).[35]

While arterial oxygen pressure at sea level is 100 mm of mercury, it slowly decreases with increasing altitude (for example, at 16,000 feet it is 40 mm of mercury). It becomes apparent why splenic infarctions associated with commercial air travel are not likely to be due to sickle cell trait.

The established incidence of the various combinations of other hemoglobins with S,[3] the established importance of the interaction of these other hemoglobins on the ability of hemoglobin-S to sickle,[34] and the benign results of the Air Corps experience with sickle cell trait,[32] suggests other possible explanations for the early case reports of splenic infarction due to high altitude flying. The very rarity of those cases suggests that what then seemed to be sickle cell trait (which is not rare) may have had a different explanation.

Genetic Counseling

If sickle cell trait is an essentially benign condition with no risk from hypoxia, the only justification for individual identification is that the bearer may participate in the production of offspring with sickle cell anemia. This is the heart of "genetic counseling" programs. It is proper to inquire into the validity of this approach.

Published data in the state of California[36] established that the total number of deaths from all hemoglobinopathies (including sickle cell anemia) during the year 1969 was 20. The California Bureau of Vital Statistics has supplied unpublished information that in 1970 there were 26 such deaths. The 1970 national census showed 1.4 million blacks in California. This would mean an estimated 140,000 with sickle cell trait and 2,800 with sickle cell anemia.

Before screening 1.4 million people in search of genetic counseling subjects in order to prevent an illness which kills less than 26 of the parent group each year, the disadvantages must be weighed against the advantages. The mass screening approach does not consider fully the possible negative effects. Sickle cell screening was made mandatory in the District of Columbia as well as Virginia and Massachusetts. In Washington, D.C., there have been reported instances where sterilization has been recommended for children as young as the age of 12 simply because they had sickle cell trait.[37] Some parts of the insurance industry have already decided health and life insurance should be denied (or only issued with high-risk premiums) to people with sickle cell trait. Adverse effects on minority hiring have already been reported. A committee of the National Academy of Sciences and National Research Council has recommended that the United States Armed Forces screen all recruits and that those with sickle cell trait not be permitted to become pilots or co-pilots[38]—this despite the available evidence which has previously been cited.

There has been no similar campaign to discourage diabetics from procreation although it could be similarly justified by geneticists. Most geneticists in sickle cell programs deny giving overt advice against having children, stating they only give information so the affected persons can make an "informed decision." This may be a euphemism for implied advice.

Recommendations

What is done should be as specific to the actual problem as possible. The immediate problem is the suffering of those afflicted with sickle cell anemia. Let us first insure that they have ready access to the best care currently available.

This can be done best by intensive education of the physicians of the country as to what is the best care. Educational programs for physicians could be sponsored and designed by state medical societies and medical schools. This

approach was used for the problem of leprosy in Hawaii, where, to be eligible to take the state licensure examination, every doctor must first complete a three- to four-hour course on leprosy given by the Health Department. Active leprosy in Hawaii has an incidence of only 6 per 100,000. Sickle cell anemia has an incidence of 14 per 100,000 in California. There are obvious differences between the two illnesses but the important point is the precedent of dealing with a unique medical problem in this unique fashion.

Second in immediacy is the problem of the still undiagnosed cases of sickle cell anemia. It would seem reasonable to have programs in which children between the ages of six months and six years would have at least one screening quantitative hemoglobin determination. Those that fall below an arbitrary point would be classed as having anemia, and then appropriate additional studies could be done to determine if the anemia was due to one of the hemoglobinopathies. If it was not, the information obtained from the screening quantitative hemoglobin determination would still be useful in taking affirmative helpful action for the patient. If sickle cell anemia or other hemoglobinopathy is found, the family and the attending physician are thus armed with important advance information that can spare the child later unnecessary discomfort. Such a program could be integrated into the programs of most well-baby clinics without undue difficulty.

Brief emphasis should be placed upon insuring that all such patient programs are voluntary. Mandatory programs for patients can easily be abused because the personnel engaged in them may lose sight of their original purpose. Voluntary programs tend to work because those participating know why they have elected to do so and see it through to its logical conclusions or leave the system when it no longer serves the client's need.

Of equal importance is the field of research. Additional research is needed into what produces a "crisis" at a given time. Additional avenues of therapy should be developed and explored.

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Refer to: Roney JG Jr: Medi-Cal—Another way (Government and Medicine). West J Med 121:83-90, Jul 1974

Medi-Cal—Another Way

JAMES G. RONEY, Jr., MD, PhD, MPH, *Los Altos, California*

THE PURCHASE OF MEDICAL CARE for persons in public assistance programs, with the advent of the Social Security amendments of 1965, became the responsibility of states, rather than of counties. County provision of care tended to be in county institutions and was usually segregated by economic, social and ethnic status. The Medicaid program proposed to purchase non-segregated care in the so-called mainstream of medicine. The Medi-Cal program is one of these Medicaid programs. Initially, it operated without many controls and it was felt to be overutilized. In 1971, the Medi-Cal Reform program began with numerous restrictions and controls specified in the amended Title 22 of the State Health and Welfare Code.

Almost all categories of participants in the Medi-Cal program are dissatisfied with it. There is abundant complaint but little constructive criticism of broad comprehension to attempt to remedy the unsatisfactory situation. This paper is a broad-stroke sketch of health care for public assistance clients in California. It grapples with the question: Given a population of eligible public assistance beneficiaries and the federal legislation in effect, what is the best way for the state to purchase health care for these clients? The paper summarizes the deficiencies of the present Medi-Cal program, suggests an alternative design based upon the available state-of-the-art in health care and discusses the implications of Medicaid programs for the private sector.

Deficiencies in the Medi-Cal Program

Neither the original Medi-Cal program nor the subsequent so-called Medi-Cal Reform has succeeded in accomplishing the aims of the Medicaid program generally nor the objectives of the reform itself. The lack of success is evidenced in the instability of leadership in the program, inability to formulate basic policies, dissatisfaction of providers and consumers, lack of cost control and the constant legislative effort to make it better through amendments to the law.

Deficiencies Relating to Program Design

The fundamental defect of the Medi-Cal program is its political rather than professional approach to health care. To meet social goals in government programs requires a fine balance between sufficient political power and adequate technical expertise. When the latter is predominant, there is knowledgeable planning but little implementation. When the former prevails, there is fearless, sometimes arrogant, implementation without realistic guidance. In some instances, a political administration may not recruit appropriate technical and professional personnel because of lack of appreciation of need. In other instances, it may be unable to do so because of philosophies incompatible with the needed professions. In either case, the result is the same.

The failure of the Medi-Cal program to make use of available technical and professional expertise in California has resulted in what might be regarded as a very expensive in-service training program for political appointees not necessarily dedicated to health care.

Another major deficiency of the program design is the unwarranted assumption that Medicaid programs may purchase care in the private sector the same way anyone else may do so. Obviously, Medicaid purchase of medical care is quite different from usual private sector purchase because

Submitted February 26, 1974.

Reprint requests to: J. G. Roney, Jr., MD, PhD, 600 University Avenue, Los Altos, CA 94022.

the clients have different needs, often cannot use the private sector system effectively and because tax funds pay for this care. As a consequence of this program design defect, Medi-Cal Reform has resulted in inappropriate barriers to health care and harassment of providers and consumers in the attempt to control costs.

The Law

Title 22 of the State Health and Welfare Code is the basis for the Medi-Cal program. That it is an unsatisfactory law is evidenced in the frequency of amendment and attempted amendment. There are several aspects of its unsatisfactory nature.

First, it is inappropriate to legislate length of hospitalization in medical care because such care varies from community to community and changes with time. Further, not all medical problems and procedures can be listed in the law. It is similarly inappropriate to include specific exclusions and inclusions of services and prices. The law governing purchase of health care for public assistance clients should be enabling legislation, specifying intent and requirements for regulations, allowing adaptability of approach from area to area. This would tend to encourage continuing evolution of the system, which is essential in so dynamic a field as health care.

Second, the law is not consistent with other state and federal law relating to health care, health manpower, health facilities, health planning, and so on.

Third, the present law gives preferential treatment to some professions.

Fourth, because of restrictions on some health professions and some levels of inpatient care, the law does not allow a comprehensive health care approach which could provide a higher quality of care with control of costs.

Implementation Deficiencies of the Medi-Cal Program

Deficiencies in implementation may be examined in terms of the government activities, providers, consumers and institutions.

Government activities

Some of the deficiencies in government operations may be identified.

(a) *The program operates without defined standards.* This is a major weakness since standard-setting is left to the judgment of individual medical consultants. A medical consultant may be conversant with standards in his own specialty but not with those of the rest of medicine. Also, his specialty standards may differ from those in the region covered by the Medi-Cal office. There is insufficient time available for medical consultants to work with medical specialty committees regarding standards. Consequently, there are confrontations between the Medi-Cal program and providers.

(b) *Communication with participants in the program is ineffective.* Many of the participants in the Medi-Cal program are unaware of policies and procedures. Recipients, providers, fiscal intermediaries and Medi-Cal program are affected by this information gap. There are frequent policy changes that are not effectively communicated to providers. It is not unusual for offices that authorize services to have policies that are not consistent with those of offices that pay for services.

(c) *Program administration is inefficient.* There is considerable duplication of effort in review of services requested for authorization and for payment. Effort is wasted in reliance on Medi-Labels, Proof of Eligibility Labels, computer technology, management slogans and formal organizational structure to solve problems, while the participants generally ignore or by-pass these program tools.

(d) *Many cost-saving efforts are unfair to the provider.* The Medi-Cal program, while purchasing "mainstream" care, does not do this at mainstream prices. Physicians, nursing homes, providers of medical devices and others are not paid the usual and customary fees or prices, but are paid a percentage of this or a fixed amount lower than the market price. In effect, these providers are asked to subsidize part of the program by absorbing the discount. This increases the cost of care which is passed on to non-Medi-Cal patients, which contributes to the increase of this segment of the Cost of Living Index in relation to other segments. Another cost-saving effort is the invocation of arbitrary rules to disallow payment of otherwise legitimate health care services.

(e) *Hidden program costs are not reflected in the annual budget.* The Medi-Cal program claims success in cost-saving since the advent of the Medi-Cal reform, but the figures cited ignore some of the hidden costs. These include government costs borne by other programs and departments such as the activities of quality assurance,

investigations, fair hearings, and the like. In addition are the out-of-pocket expenses of beneficiaries for legitimate health care services. Some providers still see public assistance beneficiaries without charge. Payment denied for services rendered and the contribution of the program to the increased cost of medical care have already been mentioned. Then, there is the added cost of doing business with Medi-Cal, especially in hospitals.

(f) *The Medi-Cal law is enforced differentially.* Although considerable savings could be made by purchasing care, particularly institutional care, at the lowest unit price, this part of the law is not enforced. In metropolitan areas where frequently there is a surplus of beds, the program has the opportunity of shopping around for lower per diem rates. The rates in one hospital may be twice those of another.

(g) *The Medi-Cal program is not coordinated with other health care programs in the same department.* The Medi-Cal program is better coordinated with the Medicare program than it is with some of the other state health care programs —for example, the Short-Doyle and Crippled Children's programs. Particularly confusing are the policies of Medi-Cal regarding psychiatric services and the policies of the Short-Doyle program, both programs administered within the Department of Health.

(h) *Provider motivation to control costs and quality of care is absent from the program.* The program has not made use of provider motivation to accomplish its goals. The reasons for lack of motivation, and even counter-motivation, to provide good care at reasonable costs are related to some of the operational and design defects mentioned earlier — for example, unfair payment mechanisms, adversary relationships, lack of standards, and ineffective communication. A properly designed health care program would enlist the aid of providers rather than antagonize them.

(i) *Promotion of prepaid health plans has not been successful.* An alternative to purchasing fee for service care for public assistance beneficiaries is contracting for such care on a capitation basis. The Medi-Cal program has encouraged this alternative, but has not been able to negotiate such contracts with many of the experienced prepaid health plan groups. Instead, it has stimulated the establishment of new, small prepaid health plans, some being outgrowths of neighborhood health centers whose federal funding was in jeopardy. To provide the comprehensive array of services in one contract at about 10 percent less than what such services have been costing on a fee for services basis is probably unrealistic, particularly in those centers where cost control has not been prominent.

Providers

In the implementation of the program, there are numerous problems with providers. Providers include primarily physicians and dentists, but other health personnel also participate—podiatrists, psychologists, chiropractors, social workers, speech therapists and others. Since much of the provision of care is under the control of the physician, this section will focus on problems of physician providers.

(a) *There are some physicians who practice poor medicine, yet are in the Medi-Cal program.* A preponderance of the sub-standard medical care is office practice, since most hospital medical staffs have some control over quality of inpatient care. Examples of sub-standard care include overuse of injections, use of ineffective drugs, use of drugs incompatible with each other or with the patient's disease, inadequate counseling of patients, inadequate follow-up or referral, and others.

(b) *There are some physicians who practice good medicine but who reject the philosophy of Medicaid programs.* Surprisingly, there are some physicians who provide good care to their private patients but do not believe that health care is a fundamental right of all. Medi-Cal patients should not be under the care of such physicians.

(c) *There are physicians who over-utilize the Medi-Cal program.* There are physicians who see many Medi-Cal patients, see them more frequently than average, and who perform a maximum of diagnostic and therapeutic services. They are obviously over-utilizing the program.

(d) *There are some physicians who refuse to see Medi-Cal patients.* Some physicians refuse to see Medi-Cal patients because the red tape and harassment intereferes with their practices. Because of this, patients are deprived of a community resource.

Other physicians have taken a modified stand. They collect the two Medi-Labels from patients early in the month, but refuse to obtain prior authorization if other visits are needed. Patients needing such care are referred to health centers

or out-patient clinics. This, of course, compounds the fragmentation of care for these patients.

(e) *There are physicians who try to "beat the system."* Some good physicians, who have been antagonized by the Medi-Cal program but still see Medi-Cal patients, try to beat the system. They have developed an informal system of behavior to circumvent the formal system required by Medi-Cal. For example, knowing that prior authorization is not required if a patient is seen after hours, many physicians have an inordinate number of after-hours patients.

Consumers

Basically, patients do not abuse the system. They may not use it properly or effectively, but that is an indication of a poorly designed system.

(a) *There are patients who do not use the program because they do not understand when it is appropriate to do so.* Some patients seek help for a medical problem which could have been handled more effectively and at less cost if seen earlier—for example, malignant or heart disease.

(b) *Some patients attempt to see several providers for the same services.* Some patients may see several physicians or other providers for the same problem, without informing the providers of this. For example, a patient may obtain therapy from more than one psychiatrist, or he may attempt to obtain several sets of dentures, glasses or hearing aids.

(c) *Some patients view part of health care as a symbol of prestige.* These patients may attempt to secure some types of health care as items of luxury or indications of status. Examples include psychoanalysis, cosmetic operations, electric wheel-chairs, and other services when these are not medically indicated.

(d) *Some patients use services frequently for social reasons.* Public assistance beneficiaries may visit out-patient clinics or physicians' offices frequently because of the need for social life, satisfied by meeting with the providers or with other beneficiaries.

Institutions

Institutional providers also have problems with the Medi-Cal program. There are some that have very few Medi-Cal patients, while others are almost totally supported by the program.

(a) *County facilities are still the primary institutional providers of care for Medi-Cal patients.* In spite of the mainstream approach in the Medi-Cal program, the county hospital and its clinics still provide the major segment of care to public assistance beneficiaries. To the extent that this occurs, health care is segregated. This is ameliorated to some extent where county facilities have begun the process of conversion to "community" hospitals.

(b) *Some institutions receive preferential treatment.* Whether for political reasons or for easy solutions to complex problems, the program is less strict with some facilities than with others in the application of criteria for levels of inpatient care.

(c) *Teaching institutions admit Medi-Cal patients who may be used in teaching and research programs.* Medi-Cal patients who receive their care in teaching hospitals tend to stay longer than comparable patients in other hospitals. The per diem rates in teaching hospitals may be twice those of other hospitals. In effect, the Medi-Cal program is subsidizing a certain part of teaching and research.

(d) *Hospitals with only acute care are penalized when patients require lesser levels of care.* The implementation of progressive patient care penalizes institutions with only acute care levels. To soften this, the Medi-Cal program will pay the lowest ward rates in the institution when it has no extended care beds. If the patient must be moved to another facility, it creates an unnecessary burden on the patient. To further complicate the picture, hospitals that wish to convert some of the acute beds to extended care beds are sometimes prohibited from doing so by the Comprehensive Health Planning Council.

(e) *Institutions that comply in a routine way with the paperwork requirements of Medi-Cal have less difficulty receiving authorization for providing services.* Some institutions have learned the proper words needed on Medi-Cal forms and they routinely satisfy these requirements and have little difficulty in receiving approval for providing services. The relationship of these forms to performance is not known. Presumably, internal controls monitor performance.

An Alternative Medi-Cal Program

In addition to the solid core of good medical care provided by the majority of health professionals for the majority of consumers, the provision of health care in any community encom-

passes some luxury medicine, sub-standard practices, ineffective treatment, varying social philosophies of providers, haphazard use of the system by consumers, little market-place competition, poor quality control of ambulatory care and lack of accessibility of care to some people. In such a market, it would be foolhardy to purchase health care for public assistance beneficiaries without some stringent contractual provisions.

The detailed design of a public assistance medical program should be the responsibility of the director of the program and his staff. Since there are a number of alternative designs, it would be inappropriate to discuss program details. However, it is appropriate to discuss the assumptions upon which such a program should be based and the functions that such a program should have.

Assumptions

Public assistance health care differs from private sector care

Public assistance health care differs from private sector care because of the source of funding, because of the special needs of public assistance clients and because of the variability of providers.

The scope of public care should exclude luxury care, unnecessary care and ineffective care, because this is not proper use of public funds. The scope should include more preventive care to offset some of the vulnerabilities of public assistance beneficiaries.

Apart from health care proper, public assistance beneficiaries need consumer guidance about how to use the complex medical system that we have. It is difficult enough for private sector patients to cope with this system; it is virtually impossible for some public assistance clients who may have language problems, lack of familiarity with mainstream medicine, accessibility problems and other difficulties. Therefore, a public assistance health care program should include a consumer guidance function in its scope of activities.

Not all licensed providers should participate in public programs. Those who practice sub-standard medicine, those who are incompatible philosophically with public assistance health care, those unwilling to accept the constraints of bureaucracy, those not willing to subject themselves to monitoring and those whose prices are not competitive, should be excluded from contracts with the program.

Standards of care for public and private sectors should be the same

Such standards should include both quality and utilization. Other things being equal, public assistance patients have the same physiological and psychological needs as private patients when afflicted with a medical problem. Therefore, comparable quality and quantity of care is indicated.

The purchase of health care for public assistance clients should be subjected to the competition of the market-place

Within the definitions of scope and quality, care should be purchased at the lowest unit cost. Providers should not be paid at a discounted rate or at arbitrary prices fixed by the state.

The state law providing the basis for Medi-Cal should be revised to reflect the alternative program

The revised law should be enabling rather than prescriptive.

The alternative program should be planned, developed, and implemented by those responsible for its direction

Those responsible for program direction should be health professionals who represent all the basic disciplines and expertise needed in such a complex program. The program should be coordinated with other health care activities of government and should be compatible with other health efforts in the community. Once in operation, the program should monitor the provision of care to ensure that quality control, cost control and compatibility of providers with the program shall continue.

Functions

If one accepts the assumptions in the foregoing section, there are a number of essential functions that should be performed in such an alternative program.

Policy making

The establishment of general policies should be the responsibility of a group composed of representatives from all types of participants in the program. These include provider organizations, fiscal intermediaries, consumers, taxpayers and government. This group would advise the director of the program at the state level. Similar groups would function at a local level.

Program development

The health professionals appointed to implement policies should plan, develop and imple-

ment the alternative program. Program development encompasses several key functions:

(a) *Specification of scope of care.* The scope of care should encompass basic community practice minus luxury, unnecessary and ineffective care plus preventive care. This determination should be made on a statewide basis and in consultation with providers of care.

(b) *Determination of quality of care guidelines.* Quality considerations should be made on a specialty basis. The preventive portion of this usually will be incremental and its provision will vary from locality to locality. Practically, the major effort will be concerned with exclusion of diagnostic and therapeutic procedures considered not acceptable in the community. In order to avoid unnecessary duplication, it would be appropriate to prepare guidelines on a statewide basis, jointly by program staff and provider specialty groups. These should then be modified as needed locally. The model treatment profiles developed and used in Santa Clara County exemplify this kind of function.

(c) *Determination of qualifications of acceptable providers.* Providers of care of the alternative program should satisfy certain criteria, jointly developed by provider organizations and program staff. These criteria should be statewide. Provider practices should conform to the local quality of care guidelines. Providers should accept the scope specifications of care. They should be compatible with the philosophy of care for public assistance clients in the Medicaid program. They should be willing to accept the bureaucratic requirements of a government program. (It is to be hoped these would be kept at a minimum.) They should feel comfortable with the monitoring of their care. They should be competitive in the pricing of their services.

These qualifications would tend, in addition to facilitating quality and cost control, to reduce unnecessary confrontations between providers and the program representatives, by eliminating the small minority of providers who are incompatible with the program. Much of the information needed for screening providers is available in computer storage of fiscal intermediaries.

(d) *Determination of eligibility criteria of public assistance beneficiaries.* A function essential to the program, of course, is the determination of who shall be eligible for health care. This is specified in the federal and state law and implemented at the county level.

Program operation

There are several types of functions in the operation of the program.

(a) *Contracting with providers.* After screening providers in the community on the basis of selection criteria and information available from fiscal intermediaries and other sources, contracts would be made with individual or group providers. Such providers would be thoroughly briefed regarding the program. Once a contract were consummated, services would be provided to eligible Medi-Cal beneficiaries without prior authorization and the provider would be paid his normal fees for these services.

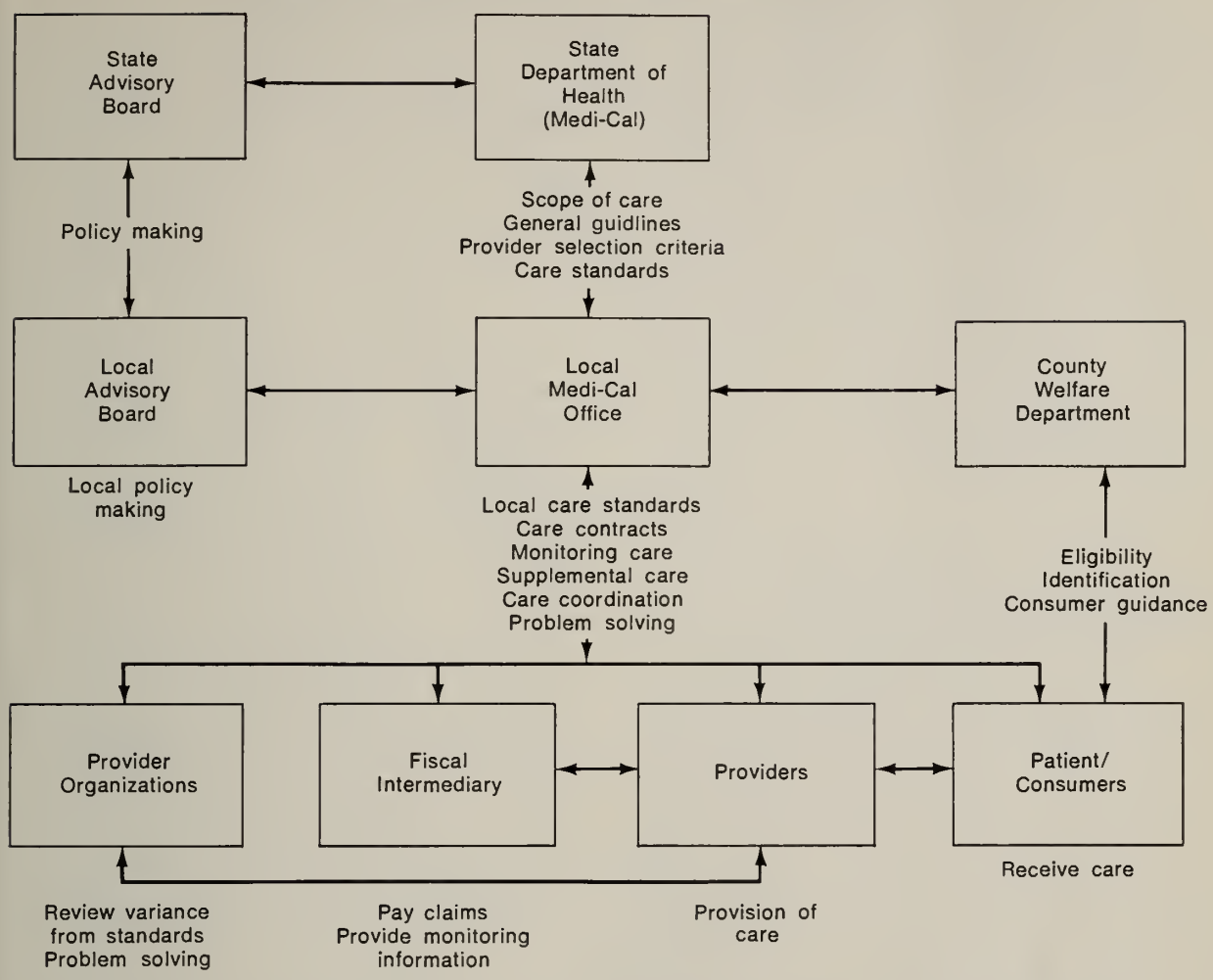
Some physician providers would be primary care physicians while others would be referral physicians. Other providers would include medical support personnel, providers of medical equipment, hospitals, nursing homes and others. Each contract would specify the range of services covered and the conditions under which they may be provided. For example, no referral physician could render care to a patient without referral from a primary care physician. Hospitalization would be under the control of either primary or referral physician. Medical equipment and transportation would be under the control of the appropriate professional personnel.

(b) *Monitoring health care.* Monitoring applies to both provider and consumer. However, since care is largely under the control of the provider, surveillance effort would be concentrated here. Monitoring supports the motivation to render service in accordance with quality and utilization standards. Variances should be reviewed by the local professional society committee integrated into the program. Monitoring also supports price control through competition of the market place. Information for monitoring should be supplied by the fiscal intermediary.

(c) *Identification of eligible beneficiaries.* Beneficiaries should have a means of identification which also indicates the category of public assistance and dates of eligibility. The system should include a method of continuous up-dating and replacement of lost identification as well as a back-up system to prevent misuse of lost or stolen identification and to identify those without identification who need care.

(d) *Guiding consumers.* Since one of the major problems with public assistance medical programs is improper use of the health care sys-

SUGGESTED CONFIGURATION OF HEALTH CARE ORGANIZATION



tem, it should be the responsibility of the program to aid consumers in the following ways:

1. *Education and motivation of the consumer for proper use of the system.* Just as providers have obligations, so do consumers. The orientation of consumers toward proper use of the system should occur at the time they become eligible. They should be advised of the differences between the Medi-Cal program and private sector care, and the reasons for these differences. The benefits of the program should be explained and they should be given the names of contracting primary physicians in the area whom they may choose as a personal physician.

2. *Coordination of care.* The local program office should be responsible for coordinating the care ordered by professional providers. Not all patients will require this. However, when the care ordered becomes complex or the resources of the primary care physician are limited, the physician should arrange with the local program office to coordinate the care.

(e) *Paying claims.* The fiscal intermediaries should pay for services rendered by contract providers for eligible Medi-Cal beneficiaries.

(f) *Problem solving.* Regardless of excellence of planning, problems will arise. Professional staff of the program working closely with the committee organization of providers should examine actual or anticipated problems, discuss alternative solutions, arrive at a consensus, and alleviate the problems.

Configuration

There are several ways in which such an alternative program could be organized. The configuration sketched in the accompanying diagram

is proposed. It is based upon modern concepts of management, trends in local government, and integration of functions outlined in the alternative program.

This kind of organization would improve communication by integrating various functioning parts at the local level. If the local program units were organized on a county basis, this would provide a better interface with local social services and with local provider organizations. Where local health and welfare agencies exist, it would be desirable to locate the local program physically in these agencies or even to contract with them to operate the local Medi-Cal program.

With fiscal intermediaries relieved of monitoring functions, payment of claims could be performed on a state-wide basis as is now planned. However, they would continue to provide monitoring information to the local program office.

Implications for the Private Sector

While the purpose of this paper is to establish a sound basis for purchasing health care for public assistance clients, the effects of such programs, regardless of excellence of design, will extend considerably further. They will affect health insurance, private sector practice, teaching institutions, comprehensive health planning and research.

Health Insurance

Once public assistance health care programs have been established on a sound basis, providing an identified essential core of care to a segment of the population, effectively and economically and of satisfactory quality, insurance companies will be affected. In the effort to control premiums, they will tend to adopt the same basic benefits packages as public programs. These will be supplemented by luxury type policies for those who wish them and can afford them.

Private Sector Medicine

Insurance companies will tend to adopt the same standards of quality and utilization as those for public programs. Since insurance companies have a wealth of computerized data about both providers and consumers, these will be used to exercise selectivity of covered benefits and control over providers. Levels of inpatient care will be chosen more judiciously by providers. Less costly equipment will be ordered for patients requiring it. Some procedures regarded as ineffective or even deleterious will not be paid for by insurance companies and will be purchased as out-of-pocket expenses of the patient. Luxury medicine will be insured in supplemental policies or will be paid for out-of-pocket.

Teaching Institutions

Since "teaching patients" have the same physiology generally as non-teaching patients, the medical care of the former will be more similar to community practice. This generally will result in fewer diagnostic procedures and shorter inpatient stay. Teaching institutions that cannot compete in quality and cost with community practice will find fewer patients being sent to them for care. The actual additional cost of education of health professionals will have to be borne by other funding mechanisms.

Comprehensive Health Planning

By subjecting health care institutions and manpower to the competition of the market place, surplus personnel and institutions will tend to move, close, or perform some other function. This would tend to support planning for health care in the community. In some instances, where communities have less than optimal resources, the same force could be operative in stimulating new institutions and manpower.

Research

Medical research is becoming increasingly constrained by considerations of patient protection in research involving "experimentation" and by cost. The public assistance programs will tend to support these trends. This will affect the momentum of some health research. In order to ensure continuation of this essential activity, research manpower and institutions will need to behave more responsibly in research that increasingly depends upon patients who are not under the control of or dependent for their care on academic/welfare institutions.

If for no other reason than the implications stated here, the health professions need to make certain that public assistance health care programs are soundly conceived, designed and developed.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

EMERGENCY MEDICAL SERVICES—Behavioral and Planning Perspectives—Edited by John H. Noble, Jr., PhD, Henry Wechsler, PhD, Margaret E. La Montagne, MSN, and Mary Anne Noble, D NSc, Behavioral Publications, 72 Fifth Avenue, New York City (10011), 1973. 595 pages, $24.95; 5 or more Student Editions, $18.95.

HEALTH EFFECTS OF ENVIRONMENTAL POLLUTION—Illustrated 24-page color booklet describing various adverse effects that the pollution of the environment has on human beings. Available free from Office of Public Affairs, Dept. MED, U.S. Environmental Protection Agency, Washington D.C. 20460.

HUMAN RADIATION BIOLOGY—Kedar N. Prasad, PhD, Associate Professor of Radiology, Chief, Section of Radiation Biology, University of Colorado Medical Center, Denver. Medical Department, Harper & Row, Publishers, Inc., 2350 Virginia Avenue, Hagerstown, MD (21740), 1974. 524 pages, $25.00.

LONG-TERM HEMODIALYSIS—The Management of the Patient with Chronic Renal Failure—Second Edition—Constantine L. Hampers, MD, Assistant Clinical Professor of Medicine, Harvard Medical School, Senior Associate in Medicine, Peter Bent Brigham Hospital, Boston; Eugene Schupak, MD, Clinical Associate Professor of Medicine, Mt. Sinai Medical School, Consultant in Nephrology, City Hospital at Elmhurst, New York City; Edmund G. Lowrie, MD, Instructor in Medicine, Harvard Medical School, Associate in Medicine, Peter Bent Brigham Hospital; and J. Michael Lazarus, MD, Instructor in Medicine, Harvard Medical School, Associate in Medicine, Peter Bent Brigham Hospital. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 243 pages, $12.50.

THE MAMMALIAN MYOCARDIUM—Edited by Glenn A. Langer, MD, Professor of Medicine and Physiology, UCLA School of Medicine; and Allan J. Brady, PhD, Professor of Physiology, UCLA School of Medicine, John Wiley & Sons, Inc., Publishers, 605 Third Avenue, New York City (10016), 1974. 310 pages, $24.50.

THE NATURAL FOOD REDUCING DIET—Harry Preston In collaboration with Emil J. Halley, MD. Books for Better Living, 21322 Lassen St., Chatsworth, CA (91311), 1974. 190 pages, $1.25 (Paperback).

THE PHYSIOLOGICAL AND CELLULAR BASIS OF METABOLIC BONE DISEASE—Howard Rasmussen, MD, PhD, Benjamin Rush Professor of Biochemistry, University of Pennsylvania School of Medicine and Senior Physician, Children's Hospital of Philadelphia; and Philippe Bordier, MD, PhD, Maitre de Recherche-INSERM, Unité de Recherche "André LICHTWITZ" Hospital Lariboisière and Rhumatologue Attaché à la Clinique Rhumatologique de l'Hopital Lariboisière (Pr. De Seze), Université Paris Nord, Paris. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1974. 364 pages, $21.50.

PROGRESS IN HEMATOLOGY—Volume VIII—Edited by Elmer B. Brown, MD; with 30 contributors. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 332 pages, $22.50.

PROGRESS IN HEMOSTASIS AND THROMBOSIS—Volume II—Edited by Theodore H. Spaet, MD, Head, Hematology Division, Montefiore Hospital and Medical Center, Professor of Medicine, Albert Einstein College of Medicine, Bronx. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1974. 372 pages, $22.50.

PROGRESS IN NEUROLOGY AND PSYCHIATRY—An Annual Review—Volume XXVIII—Edited by E. A. Spiegel, MD, Dr Med (Hon), Emer. Professor and Head of the Department of Experimental Neurology, Temple University School of Medicine, Philadelphia. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1974. 494 pages, $29.75.

RAPE—How to Avoid It and What to Do About It If You Can't—June Bundy Csida and Joseph Csida. Books for Better Living, 21322 Lassen St., Chatsworth, CA (91311), 1974. 238 pages, $1.50 (Paperback).

STOP WITHOUT QUITTING—Joseph Danysh. International Society for General Semantics, 509 Sansome Street, P.O. Box 2469, San Francisco (94126), 1974. 120 pages, $4.95 (Paperback).

SURGICAL PATHOLOGY—Fifth Edition—Lauren V. Ackerman, MD, Professor Emeritus of Surgical Pathology and Pathology, Washington University School of Medicine, St. Louis, Professor of Pathology, State University of New York at Stony Brook; and Juan Rosai, MD, Associate Professor of Pathology, Washington University School of Medicine, Associate Surgical Pathologist, Barnes and Affiliated Hospitals, St. Louis. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis (63103), 1974. 1394 pages, with 1329 figures, $45.50.

TUMORS OF THE HEAD AND NECK—Clinical and Pathological Considerations—John G. Batsakis, MD, Professor of Pathology, The University of Michigan Medical Center, Ann Arbor. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202)), 1974. 388 pages, $19.75.

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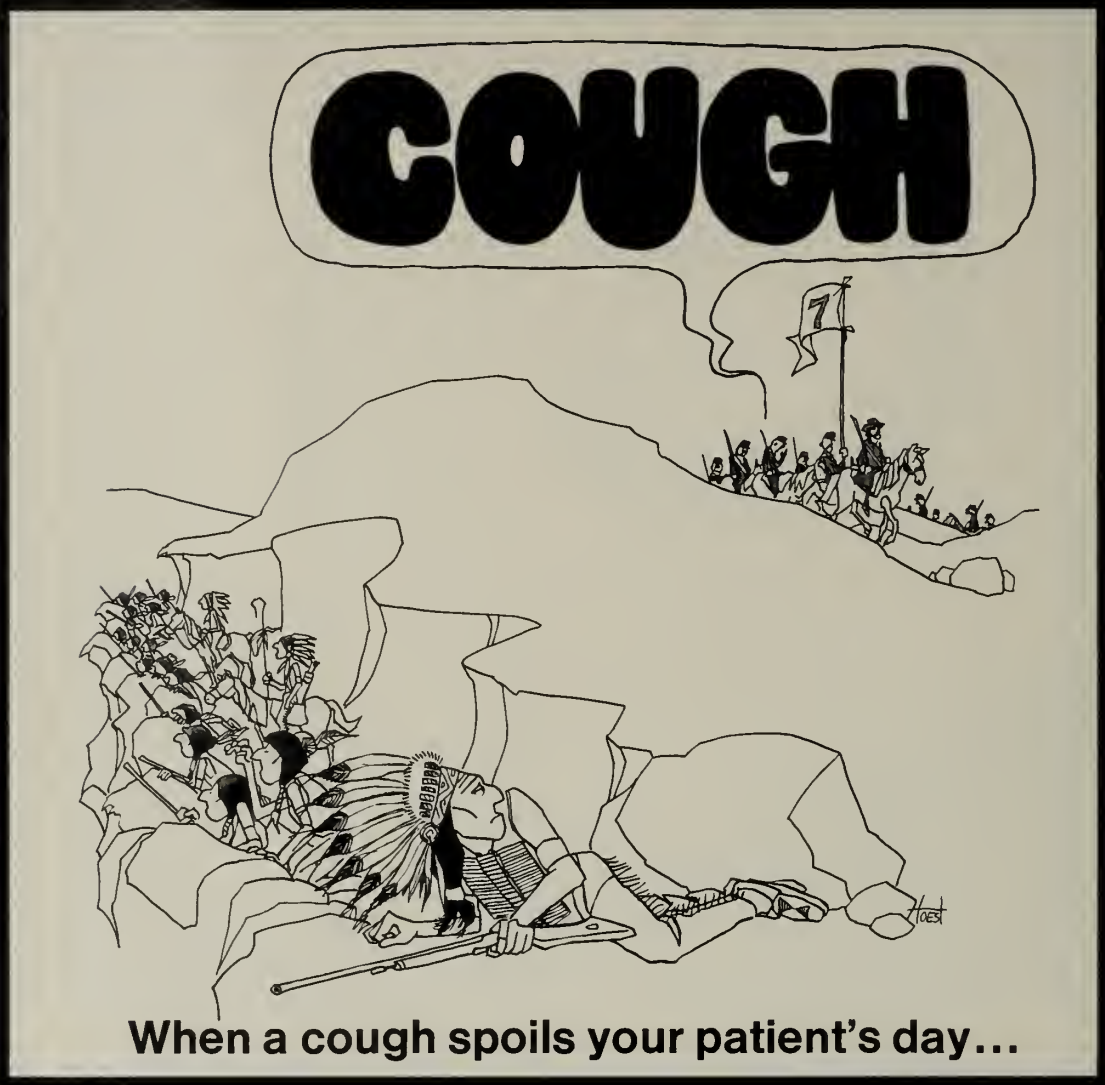

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California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine**, Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

July 22-25—**Cancer of the Skin and Mouth—Advances in Diagnosis and Treatment.** STAN. Monday-Thursday. 28 hrs. $200.

September 7-8—**Toward the Earlier Detection of Breast Cancer.** UCLA. Saturday-Sunday.

September 14—**Breast Cancer Update 1974.** American Cancer Society, Northeast Los Angeles County Unit, at Hilton Hotel, Pasadena. Saturday. 6 hrs. $20. Contact: Hilario R. Liras, Ed. Dir., ACS, 230 N. Lake Ave., No. 1, Pasadena 91101. (213) 795-7774.

September 27-28—**Bone Cancer: The Multidiscipline Disease.** West Coast Cancer Foundation at St. Francis Hotel, San Francisco. Friday-Saturday. $75. Contact: Jerome M. Vaeth, MD, Dir., WCCF, 2200 Hayes St., San Francisco 94117.

October 2—**Urological Cancer Conference.** American Cancer Society and Los Angeles County Urological Society at Century Plaza Hotel, Los Angeles. Wednesday. Contact: William H. Tanner, Dir., Professional Ed., ACS, 2932 Wilshire Blvd., Santa Monica. (213) 828-7474.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists (UCLA faculty members) in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John R. Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

July 27—**New Concepts in Respiratory Therapy Management.** UCD. Saturday.

August 7—**Review of Internal Medicine.** PMC at Presbyterian Hospital, San Francisco. Through October 2; Wednesdays, 7-10 p.m. For physicians planning ABIM recertification exam. $25 for each session; $20 each if registered for 4 or more. Aug. 7—Infectious Diseases; Aug. 14—Cardiology; Aug. 21—Neurology; Aug. 28—Hematology; Sept. 4—Nephrology; Sept. 11—Pulmonary Diseases; Sept. 18—Gastroenterology; Sept. 25—Rheumatology; Oct. 2—Endocrinology.

August 25-31—**An In-Depth Nephrology Board Review Course.** Cedars-Sinai Medical Center at Beverly Hilton Hotel, Los Angeles. Sunday-Saturday. $150. Contact: Drs. Morton H. Maxwell and Andrew J. Lewin, Div. of Nephrology & Hypertension, Mt. Sinai Hospital, 8720 Beverly Blvd., Los Angeles 90048.

September 19-21—**The Relevance of Animal Models to Human Dermato-Pharmacology and Dermato-Toxicology.** UCSF. Thursday-Saturday. 11 hrs. $200.

September 21—**Course in Armchair Allergy.** PMC. Saturday.

October 2-5—**Present Concepts in Internal Medicine.** Letterman Army Medical Center, San Francisco. Wednesday-Saturday. 24 hrs. Contact: John J. Deller, C, Dept. of Medicine, Letterman Army Med. Ctr., Presidio, San Francisco 94129. (415) 561-4275.

October 3-4—**Coronary Care.** USC. Thursday-Friday.

October 5-6—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 5-6—**Dermatologic Surgery.** See Surgery, October 5-6.

October 7-8—**Endocrine Review.** USC. Monday-Tuesday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1975—date and place to be announced.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: Los Angeles Convention Center, Los Angeles, February 22-26, 1975.

Hawaii Medical Association—510 S. Beretania St., Honolulu 96813. Annual Meeting—Ilikai Hotel, Honolulu, October 28-November 2, 1974.

Idaho Medical Association—407 W. Bannock St., Boise 83702. Annual Meeting: Lodge, Sun Valley, July 24-27, 1974.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: Big Sky of Montana, Big Sky, September 12-14, 1974.

Nevada State Medical Association—3660 Baker Lane, Reno 89501. Annual Meeting: Stockmen's, Elko, September 27-29, 1974.

Oregon Medical Association—2164 SW Park Pl., Portland 97205. Annual Meeting: Hilton Hotel, Portland, September 11-15, 1974.

Washington State Medical Association—444 NE Ravenna Blvd., #108, Seattle 98115. Annual Meeting: Davenport Hotel, Spokane, September 22-25, 1974.

October 7-11—**Common Problems in Primary Care.** See Of Interest to All, October 7-11.

October 8—**Paul M. Aggeler Visiting Professor—5th Annual.** UCSF at San Francisco General Hospital. Tuesday, 11:00 a.m-12:00 noon. Judith G. Pool, Ph.D., Stanford, will talk on her research on hemophilia during a year's sabbatical at Oxford Univ. Contact: Susan Nutter, S.F. Gen. Hosp., San Francisco. (415) 648-8200, ext. 404.

October 9-11—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

October 17-20—**California Society of Internal Medicine—Annual Meeting.** Ahwahnee Hotel, Yosemite. Thursday-Sunday. 8 hrs. Contact: Carol H. Handley, Exec. Dir., CSIM, 1412 Central Towers, 703 Market St., San Francisco 94103. (415) 362-1548.

October 18—**Recent Advances in Rheumatology.** UCD at Woodlake Inn, Sacramento. Friday.

October 18-19—**San Diego County Heart Association.** Sheraton-Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Mrs. Cathy Ware, Prog. Dir., SDCHA, 3640 Fifth Ave., P.O. Box 3625, San Diego 92103. (714) 291-7454.

October 19-20—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 24-26—**Non-Invasive Cardiovascular Procedures.** USC. Thursday-Saturday.

October 24-26—**West Coast Allergy Society—13th Annual Scientific Program.** St. Francis Hotel, San Francisco. Thursday-Saturday. 19 hrs. $25 for members; $30 non-members. Contact: Daniel K. Billmeyer, MD, Prog. Chr., 2164 S.W. Park Pl., Portland 97205. (503) 226-1555.

October 25—**Emergency Respiratory Care for Health Related Professions.** PMC. Friday.

October 25-26—**Clinical Gastroenterology.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. Contact: Williamson B. Strum, MD, Div. of Gastroenterology, Scripps Clinic & Research Foundation, 476 Prospect St., La Jolla 92037.

Continuously—**Recertification Review Course—Internal Medicine.** USC at Louis B. Mayer Medical Teaching Center, Keith Admin. Bldg. Tuesdays and Thursdays, 7-10 p.m. April 9-October 10, 1974. Sessions will cover 9 broad topics of internal medicine; each topic will have 5 evening sessions.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Cardiology Conferences.** San Diego County Heart Association at Sharp Hospital, San Diego. Fridays, 8-10 a.m. Contact: William Kuzman, MD, Sharp Hospital, 7901 Frost St., San Diego. (714) 277-6121. Or Mrs. Cathy Ware, SDCHA, P.O. Box 3625, San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 294-5663. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conference.** Thursdays, 8:00 p.m. **Cardiosurgical Conference.** Fridays, 2:00 p.m. UCSD at University Hospital, San Diego.

Continuously—**Medical Mortality Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Fridays, 11:30 a.m.

Continuously—**Medical Chest Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

Continuously—**Medical-Surgical G.I. Conference.** UCSD at University Hospital, 3rd floor, rm 3, San Diego. Tuesdays, 12:30 p.m.

Continuously—**Hematology Pathology/Hematology Morphology Conference.** Mondays, 11:00 a.m. **Hematology Clinical Conference.** Mondays, 12 noon. UCSD alternating between University and VA Hospitals, San Diego.

Continuously—**Gastroenterology Conference.** Tuesdays, 11:00 a.m. **Gastrointestinal Conference.** Tuesdays, 12:30 p.m. **Gastroenterology-Pathology Conference.** Wednesdays, 11:00 a.m. UCSD at University Hospital, San Diego.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Preceptorships in Cardiology.** PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Continuously—**Preceptorships in Practical Office Dermatology.** PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

ontinuously—**Preceptorships in Infectious Disease.** PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

ontinuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ontinuously—**Renal Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

ontinuously—**Rheumatology Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. 2nd and 4th Fridays, 12:30 p.m.

ntinuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ntinuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of every other month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

ontinuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

ontinuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1534.

ontinuously—**Training for Physicians in General Internal Medicine.** LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

ontinuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

and Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Dermatology. 11:00 a.m. VA Hospital, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

8:30 a.m., Auditorium, Brown Bldg., Mt. Sinai Hospital, Los Angeles. UCLA.

Dermatology. 10:00 a.m. University Hospital, San Diego. UCSD.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:00 noon. Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., VA Hospital, San Diego. UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:00-10:00 a.m., 4th Floor, UCLA Medical Center. UCLA.

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30-10:00 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

MENTAL RETARDATION

September 29-October 11—**Mental Retardation.** UCLA. 13 days.

OBSTETRICS AND GYNECOLOGY

September 19-21—**Biology and Pathology of Pregnancy and the Neonatal Period.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

October 9-11—**Fetal Monitoring.** USC. Wednesday-Friday.

October 12—**Prenatal Nutrition—Workshop for Physicians.** Calif. Association for Maternal and Child Health at Sheraton Inn, San Diego. Saturday. Contact: Carol G. Corruccini, M.S., 425 University Ave., No. 6, Davis 95616. (916) 756-8471.

October 14-15—**New Horizons in Perinatal Intensive Care.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. 13 hrs. $125. Contact: Bonnie Stapleton, Cont. Ed. Coord., Harbor Gen. Hosp., 1124 W. Carson, Torrance 90502. (213) 775-7711, ext. 1373.

October 16-19—**Ob-Gyn Review.** USC. Wednesday-Saturday.

October 20-23—**International Family Planning Research Association.** Gene Autry Hotel, Palm Springs. Sunday-Wednesday. Contact: Ludwig Lauerhass, Exec. Dir., 2960 W. 8th St., Los Angeles 90005. (213) 386-1970.

Continuously—**Ob-Gyn Case Review.** Saturdays, 8:00 a.m. **Gyn Tumor Conference/Mortality Conference.** Wednesdays, 12:30 p.m. **Ob-Gyn Pathology Conference.** Wednesdays, 4:00 p.m. UCSD at University Hospital, San Diego.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

8:00-9:00 a.m., Fourth Floor Auditorium, UCLA Medical Center. UCLA.

5:00 p.m. Pickard Auditorium, University Hospital, San Diego. UCSD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

PEDIATRICS

September 11-12—**Brennemann Memorial Lectures—31st Annual.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Mrs. Eva Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 13-14—**Endocrinology in the Pubescent and Adolescent.** Children's Hospital Medical Center, Oakland, at Highlands Inn, Carmel. Friday-Saturday. 8 hrs. $50. Contact: Inetta Carty Calori, Children's Hosp. Med. Ctr., 51st & Grove Sts., Oakland 94609. (415) 654-5600.

October 7-11—**Common Problems in Primary Care.** See Of Interest to All, October 7-11.

October 14-15—**New Horizons in Perinatal Intensive Care.** See Obstetrics and Gynecology, October 14-15.

October 19-23—**American Academy of Pediatrics.** Hilton Hotel, San Francisco. Saturday-Wednesday. Contact: Robert G. Frazier, MD, Exec. Dir., 1801 Hinman Ave., Evanston, Ill. 60204.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD. Small Conference Room, University Hospital, San Diego. Fridays, 12:30 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., and Fridays, 9:30-11:00 a.m., Conference Room 3. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Fourth Thursday of each month, 2:00 p.m., Main Doheny Conference Room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Continuously—**Pediatric Immunology and Allergy Seminar.** UCSD. Wednesdays, 8:00 a.m.

Continuously—**Pediatric Neurology.** UCSD at University Hospital, 3rd floor, rm. 3, San Diego. 1st and 3rd Wednesdays, 12:30 p.m.

Continuously—**Pediatric-Radiology-Urology Conference.** UCSD at University Hospital, Radiology Conference Room, San Diego. 1st and 3rd Fridays, 4:00 p.m.

Grand Rounds—Pediatrics

Tuesdays

Pediatric Cardiology. 7:30 a.m. University Hospital, San Diego. UCSD.

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Pediatric Infectious Disease. 1:30 p.m. University Hospital, San Diego. UCSD.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:30 a.m., Lecture Room, A Floor, Health Sciences Center UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m. 5th floor Ward, St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

SYCHIATRY

ctober 24-27—**American Academy of Child Psychiatry.** Fairmont Hotel, San Francisco. Thursday-Sunday. Contact: American Academy of Child Psychiatry, 1800 R Street, NW, Washington, D.C. 20009.

ontinuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ontinuously—**Seminar in Ambulatory Methods.** UCSD at Mental Health Clinic, San Diego. Mondays, 11:00 a.m.

ontinuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

rand Rounds—Psychiatry

Tuesdays
8:30 a.m. VA Hospital, Rm. 2010, San Diego. UCSD.

Wednesdays
10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays
11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

ADIOLOGY AND PATHOLOGY

ptember 22-23—**Society for Pediatric Radiology.** Hilton Hotel, San Francisco. Sunday-Monday. Contact: John P. Dorst, MD, Johns Hopkins Hospital, Baltimore, Md. 21205.

ptember 24-27—**American Roentgen Ray Society.** Hilton Hotel, San Francisco. Tuesday-Friday. Contact: Ted F. Leigh, MD, Emory University Clinic, Atlanta, Ga. 30322.

ctober 25-26—**Society of Nuclear Medicine, Northern & Southern California Chapters—Annual Meeting.** Hilton Hotel, San Francisco. Friday-Saturday. Contact: Society of Nuclear Medicine, No. Calif. Chapter, 1595 Soquel Dr., Santa Cruz. (408) 476-7300.

ontinuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ontinuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ontinuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ontinuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ontinuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward I. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

ontinuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

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6117 Malt Avenue, Los Angeles, Ca 90040

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Continuously—**Medical X-Ray Conference.** Monday-Friday, 9:30 a.m. (Wednesdays, 8:30 a.m.). **Diagnostic X-Ray Review.** Wednesdays, 3:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Radiology/Pathology Conference.** UCSD at University Hospital, Pickard Amphitheatre, San Diego. Thursdays, 12:30 p.m.

Continuously—**G.I. Radiology Conference.** Fridays, 1:00 p.m. **Pediatric Radiology Conference.** Thursdays, 4:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Neuroradiology Conference.** UCSD at University Hospital, San Diego, Tuesdays, 4:30 p.m. and at VA Hospital, San Diego, Wednesdays, 2:00 p.m.

Continuously—**Ortho-Radiology Conference.** UCSD at VA Hospital, San Diego. Fridays, 8:00 a.m.

Continuously—**Radiology-Urology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 3:30 p.m.

Continuously—**Pathology Review.** Wednesdays, 9:30 a.m. **Cardiovascular Pathology Conference.** Tuesdays, 8:00 a.m. **Pathology-Urology Conference.** Alternate Mondays, 4:30 p.m. UCSD at University Hospital, San Diego.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

July 18-19—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

July 25-27—**Phaco-Emulsification.** St. John's Hospital and Southern California Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

August 3—**New Surgical Techniques in Strabismus.** Harbor General Hospital, Torrance. Saturday. 5 hrs. $35. Contact: Mrs. Bonnie Stapleton, Cont. Ed. Coord., Harbor Gen. Hosp., 1124 W. Carson St., Torrance 90502. (213) 775-7711, ext. 1373.

August 7-9—**Kerotoplasty.** PMC at Univ. of the Pacific Dental School, San Francisco. Wednesday-Friday. 20 hrs. $150; $75 for residents.

August 8-9—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

August 14-18—**Urology.** UCLA. At UC Conference Center, Lake Arrowhead. Wednesday-Sunday.

August 15-16—**Ophthalmic Skills.** PMC at Univ. of the Pacific Dental School, San Francisco. Thursday-Friday.

September 10-13—**Life Saving Measures for the Critically Injured.** See Of Interest to All, September 10-13.

September 12-13—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

September 26-28—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

September 26-28—**Cerebral Palsy—New Perspectives.** American Academy for Cerebral Palsy at Children's Hospital at Stanford. Thursday-Saturday. $75. Contact: E. E. Bleck, MD, Children's Hospital at Stanford, 520 Willow Rd., Palo Alto 94304.

September 26-28—**The Neck.** American Academy of Orthopaedic Surgeons. Anaheim. Thursday-Saturday. $150 for physicians; $50 residents. Contact: E. Shannon Stauffer, MD, Rancho Los Amigos Hospital, Downey 90242.

October 5-6—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

October 5-12—**Western Orthopedic Association.** Hawaii. One week. Contact: Ms. H. Jacqueline Martin, Exec. Sec., WOA, 354 21st St., Oakland 94612.

October 17-18—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 17-19—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

October 31-November 1—**Strabismus.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday.

Continuously—**Anesthesia Lecture Series.** UCSD at University Hospital, 3rd floor conference room, San Diego. Wednesdays, 4:45 p.m.

Continuously—**Anesthesiology Mortality and Morbidity Conference.** UCSD at VA Hospital, Rm. 6006, San Diego. Thursdays, 4:30 p.m.

Continuously—**Neurological Sciences.** St. Francis Hospital, Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens of current material and review of current topics in specialty. Weekly notification of cases available. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital, 3630 Imperial Highway, Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Science Lecture Series.** Dept. of Surgery, St. Mary's Hospital, San Francisco. Mondays, 11:15 a.m.-12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Postgraduate traineeships of 4-14 days duration, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at St. Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser San Francisco, and Harkness Memorial Hospitals. Third Tuesday of each month, 6:00 p.m. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at Los Angeles County-USC Medical Center. Mondays, 7:00-9:00 p.m. Contact: Dept. of Orthopedics, USC School of Med., 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arrangement.

ontinuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

ontinuously—**Surgical Anatomy.** St. Mary's Hospital, San Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Classroom. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ontinuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ontinuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ntinuously—**Surgical Mortality and Morbidity Conference.** UCSD alternating between University and VA Hospitals, San Diego. Saturdays. 9:30 a.m.

ontinuously—**Ortho Surgical Conference.** UCSD at University Hospital, 3rd floor conference room, San Diego. Wednesdays, 8:00 a.m.

ntinuously—**Otolaryngology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Fridays, 8:30 a.m.

ntinuously—**Laryngeal Physiology.** UCSD at VA Hospital, San Diego. Fridays, 8:30 a.m.

ontinuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

ontinuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ontinuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ntinuously—**Trauma Conference.** UCSD at University Hospital, 1st floor conference room, San Diego. Tuesdays, 3:30 p.m.

ntinuously—**Vascular Surgery Conference.** UCSD alternating between VA and University Hospitals, San Diego. Thursdays, 4:00 p.m.

ntinuously—**Radiology-Urology Conference. Pathology-Urology Conference.** See Radiology and Pathology, Continuously.

ntinuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

and Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Lebanon Hall Auditorium, Cedars-Sinai Hospital, Los Angeles. UCLA.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and Neurosurgery. 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Otolaryngology. 12:00 noon. University and VA Hospitals, San Diego. UCSD.

Neurology, Neuropathology, Neurosurgery. 4:00 p.m. University and VA Hospitals, San Diego. UCSD.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital, 1st, 3rd, 5th Sat.; VA Hospital, 2nd, 4th Sat., San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

August 17-28—**Postgraduate Refresher Course—17th Annual.** USC at Hawaii. 12 days. $225.

August 21-25—**Family Practice Refresher Course.** UCLA and Santa Monica Med. Center at Beverly Hilton Hotel, Los Angeles. Wednesday-Sunday.

August 25-30—**Family Practice Refresher Course.** UCD at Squaw Valley. Sunday-Friday.

August 26-30—**Computer Applications in Medical Practice—A Guided Tour.** USC Schools of Medicine and Engineering. Monday-Friday. $375. Contact: Dir. of Continuing Engineering Education, USC, Powell Hall 212, Code D, University Park, Los Angeles 90007.

September 3-8—**Family Practice Review Course—5th Annual.** UCI. Tuesday-Sunday. 44 hrs.

September 9-13—**Emergency Medicine.** UCSF. Monday-Friday.

September 10-13—**Life Saving Measures for the Critically Injured.** UCLA. Tuesday-Friday.

September 12-14—**Emergency Care.** UCSF. Thursday-Saturday.

September 20—**The Role of Nutrition in Medicine.** UCD. Friday.

September 21-22—**Acupuncture.** UCLA. Saturday-Sunday.

October 3-5—**American Medical Writers Association—34th Annual Meeting.** Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. Contact: American Medical Writers Assn., 9650 Rockville Pike, Bethesda, Md. 20014.

October 7-11—**Common Problems in Primary Care.** STAN. Monday-Friday. A review course for family physicians, gen. internists and gen. pediatricians.

October 10-12—**Western Industrial Health Conference—18th Annual.** Western Industrial Medical Association at Hilton

Hotel, Los Angeles. Thursday-Saturday. Contact: Mr. B. H. Bravinder, Exec. Sec., P.O. Box 201, Alamo 94507. (415) 837-0874.

October 12—**Hypertension.** USC. Saturday.

October 14-17—**American Academy of Family Physicians—Annual Scientific Assembly.** Los Angeles Convention Center. Monday-Thursday. Contact: Edward E. Daleske, Sec., Comm. on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, Mo. 64114. (816) 333-9700.

October 23—**Ethical Aspects of Experimentation with Human Subjects.** USC. Wednesday.

October 28-November 1—**Intensive Care.** STAN. Monday-Friday.

October 28-November 2—**Hawaii Medical Association.** Ilikai Hotel, Honolulu. Tuesday-Friday. Contact: Mr. H. Tom Thorson, Exec. Dir., 510 S. Beretania St., Honolulu 96813.

Continuously—**Emergency Care.** USC. September 17-December 3. Tuesdays, 7:30-10:00 p.m.

Continuously—**Bedside Clinics.** USC. September 26-December 19. Thursdays, 7:30-9:30 p.m.

Continuously—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. October 1-December 3. Tuesdays (except Nov. 5 and 12).

Continuously—**Clinical Conferences.** UCSF at Community Hospital, Santa Cruz. October 9, 1974-June 11, 1975. Wednesdays.

Continuously—**Continuing Medical Education Noon Conferences.** The Hospital of the Good Samaritan, Los Angeles. Every weekday, 12-1 p.m. For monthly calendar, contact: Janie Sternal, Coord., Cont. Med. Ed., Hosp. of the Good Samaritan, 1212 Shatto St., Los Angeles 90029. (213) 482-8111.

Continuously—**Clinical Problems in Daily Practice: Physiological Basis and Practical Management.** UCSF at Chinese Hospital, San Francisco. 1st Tuesday of each month; 8:00-9:30 p.m. July—Diabetes Mellitus; Aug.—Congestive Heart Failure; Sept.—Jaundice; Oct. & Nov.—to be announced.

Continuously—**Emergency Room Lecture Series.** UCSD at University Hospital, San Diego. Wednesdays, 10:00 a.m.

Continuously—**Endocrinology, Metabolism, Reproductive Medicine, Genetics Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 11:30 a.m.

Continuously—**Preceptorships in International Health, Microbiology, Pharmacology and Experimental Therapeutics, Physiology.** UCSF. By special arrangement.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange County Chapter, American Academy of Family Physicians at Saddleback Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; La Palma Intercommunity Hosp., La Palma; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Riviera Hosp., Torrance; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $1[illegible] per session. Contact: William J. Newman, MD, P.O. Box [illegible] Sonoma 95476. (707) 996-3621.

Continuously—**Basic Science Seminar.** UCSD Wednesday [illegible] 9:15 a.m., University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 9005[illegible] (213) 483-3451.

Continuously—**Medical Media Network.** Programs and study guides produced in association with faculties of major medical schools and centers throughout the U.S. MMN administered by University Extension, UCLA. Rental or purchase, 16 mm, super 8 mm, videotape and video-cassette. Provides physicians with current educational programs. Contact: Ms. Jan MacAllister, Distribution Mgr., MMN, 1099 Le Conte Ave., Room 540, Los Angeles 90024. (213) 82[illegible] 7781.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

September 11-15—**Oregon Medical Association 100th Annual Session.** Portland Hilton Hotel. Contact: James Kronenberg, Associate Executive Director, OMA, 2164 SW Park Place, Portland 97205.

OBSTETRICS AND GYNECOLOGY

October 6-10—**Pacific Coast Obstetric and Gynecological Society,** Bend. Contact: M. W. Breese, MD, 1133 SW Market Street, Portland 97205.

SURGERY

September 27-October 3—**International College of Surgeons Western Hemisphere Congress,** Portland. Contact: M. [illegible] Brodney, 1516 N Lake Shore Drive, Chicago, IL 60610.

INTEREST TO ALL PHYSICIANS

gust 16-17—**John Tomlin Memorial Cancer Lectures,** Rogue Valley Country Club, Medford. 12:30-5:00 pm, Friday; 9:00 am-1:00 pm, Saturday. Contact: American Cancer Society, Oregon Division, Inc., SW Area Unit, Box 698, 212 Leverette Building, Medford 97501

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tober 16-19—**American Society of Human Genetics,** Portland. Contact: W. E. Nance, MD, Medical Genetics, Indiana University Medical Center, Indianapolis, IN 46202.

ASHINGTON, MONTANA, LASKA and IDAHO

y 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Contact: Armand L. Bird, Executive Director, IMA, 407 W. Bannock Street, Boise 83702. (208) 344-7888.

tember 12-15—**Montana State Medical Association Annual Meeting.** Big Sky of Montana, Big Sky. Contact: G. Brian Zins, Executive Director, MSMA, 2021 11th Avenue—Suite 12, Helena 59601. (406) 443-4000.

tember 22-25—**Washington State Medical Association Annual Meeting.** Davenport Hotel, Spokane. Contact: Harlan R. Knudson, Executive Director, WSMA, 444 NE Ravenna Boulevard—#108, Seattle 98115. (206) LA 3-9110.

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n order to have future activities listed here or to receive nformation on these and other activities, please write Ms. oan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

e 12-August 28—**Expo '74—Topics in Medicine.** Every Wednesday morning for 12 weeks. Deaconess Hospital, pokane. 3 hrs. per session. $10 per session; $90 for 12 sessions. Contact Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305, HSB, SC-50, Seattle 8195. (206) 543-1050.

y 25-27—**American Electroencephalographic Society.** Thursday-Saturday. Washington Plaza, Seattle. Contact: Mrs. Margaret H. Henry, 36391 Maple Grove Rd., Willoughby Hills, Ohio 44094.

y 29-31—**World of the Heart and Lung.** Monday-Wednesday. Seattle. Fee not set. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305, HSB, SC-50, Seattle 98195. (206) 543-1050.

gust 20-25—**Northwest Protologic Society.** Tuesday-Sunday. pokane. Contact: Edward Clanton, MD, West 904 Bishop Court, Spokane 99204.

tember 13-14—**Clinical Cancer Conference.** Friday-Saturday. Edgewater Inn, Seattle. 13 hrs. $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

tember 13-14—**Ophthalmology for the Non-Ophthalmologist.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., eattle 98101. (206) MA 3-3700, Ext 470.

tember 27-28—**Arthritis Days '74.** Friday-Saturday. Seattle. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, C-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 43-1050.

Index to The Western Journal of Medicine Advertising

Bank of America 19

Books Received 18

Breon Laboratories Inc.
Bronkotabs 9

Burroughs Wellcome Co.
Empirin Compound/Codeine 17

Classified 14, 15

Compton Foundation 14

Dorsey Laboratories
Triaminic Expectorant 20

Geigy Pharmaceuticals
Tofranil-PM 6, 7, 8

Eli Lilly and Company
Kefzol 16

Mead Johnson Laboratories
Vasodilan 4

Asociación de Médicos Mexicanos, A.C.
Hotel-Club Venture in Mazatlan 18

Pharmaceutical Manufacturers Association
Prescription ads 12, 13

Presto Food Products, Inc.
Mocha Mix ..... 4th Cover

Roche Laboratories
Dalmane ..... 2nd Cover and Page 1

Safeguard Business Systems Inc 25

G. D. Searle & Co.
Pro-Banthine ..... 30 and 3rd Cover

Security Pacific Bank 10

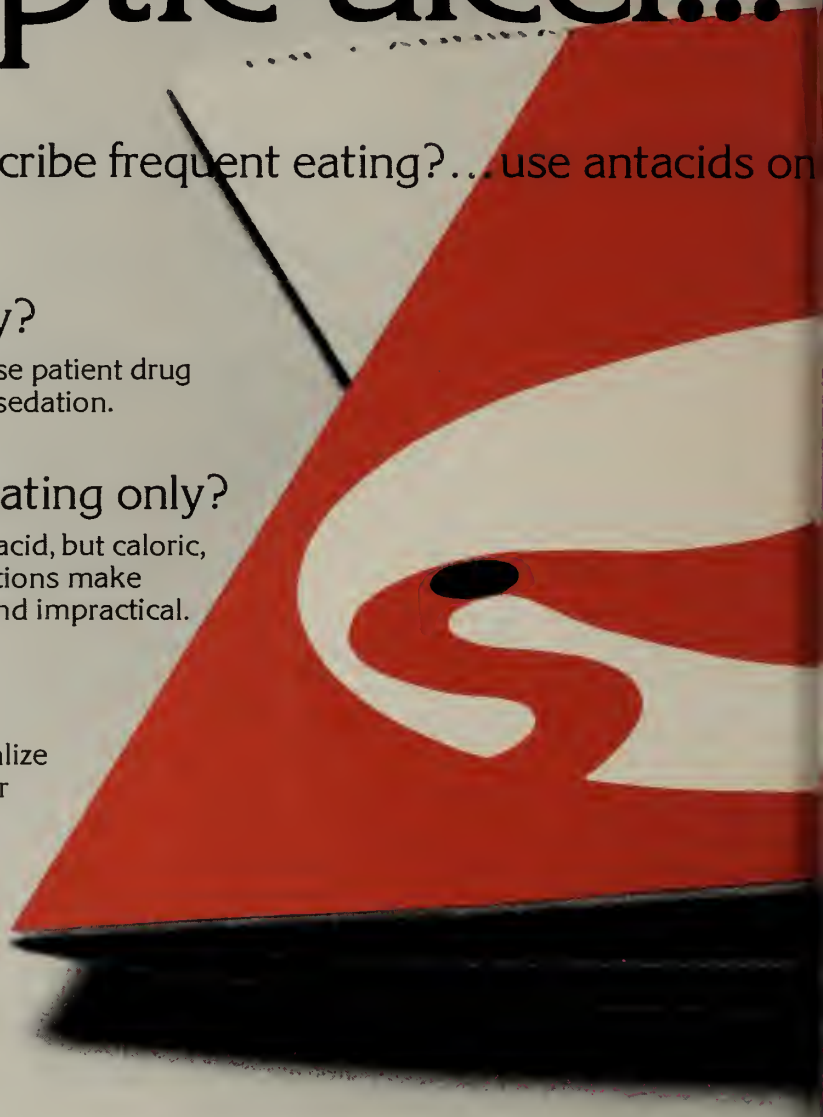
Smith, Kline & French Co.
Dyazide 11

State Compensation Insurance Fund 3

United State Air Force
Placement 5

how to civilize the of peptic ulcer...

give pain killers?...prescribe frequent eating?...use antacids on



give pain killers only?

They relieve pain but may cause patient drug dependency and unnecessary sedation.

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Frequent feeding helps buffer acid, but caloric, digestive, and social considerations make frequent eating both difficult and impractical.

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Warnings: Patients with severe cardiac disease should be given this medication with caution.

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Adverse Reactions: Varying degrees of drying of salivary secretions

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Helps to relieve pain without risk of patient drug dependency.

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Reduces gastric secretory volume and total resting and free acid without the caloric, digestive, and social problems occasioned by frequent eating.

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*Fordtran, J. S., and Collyns, J. A. H.: Antacid Pharmacology in Duodenal Ulcer: Effect of Antacids on Postcibal Gastric Acidity and Peptic Activity, New England J. Med. 274:921-927 (April 28) 1966.

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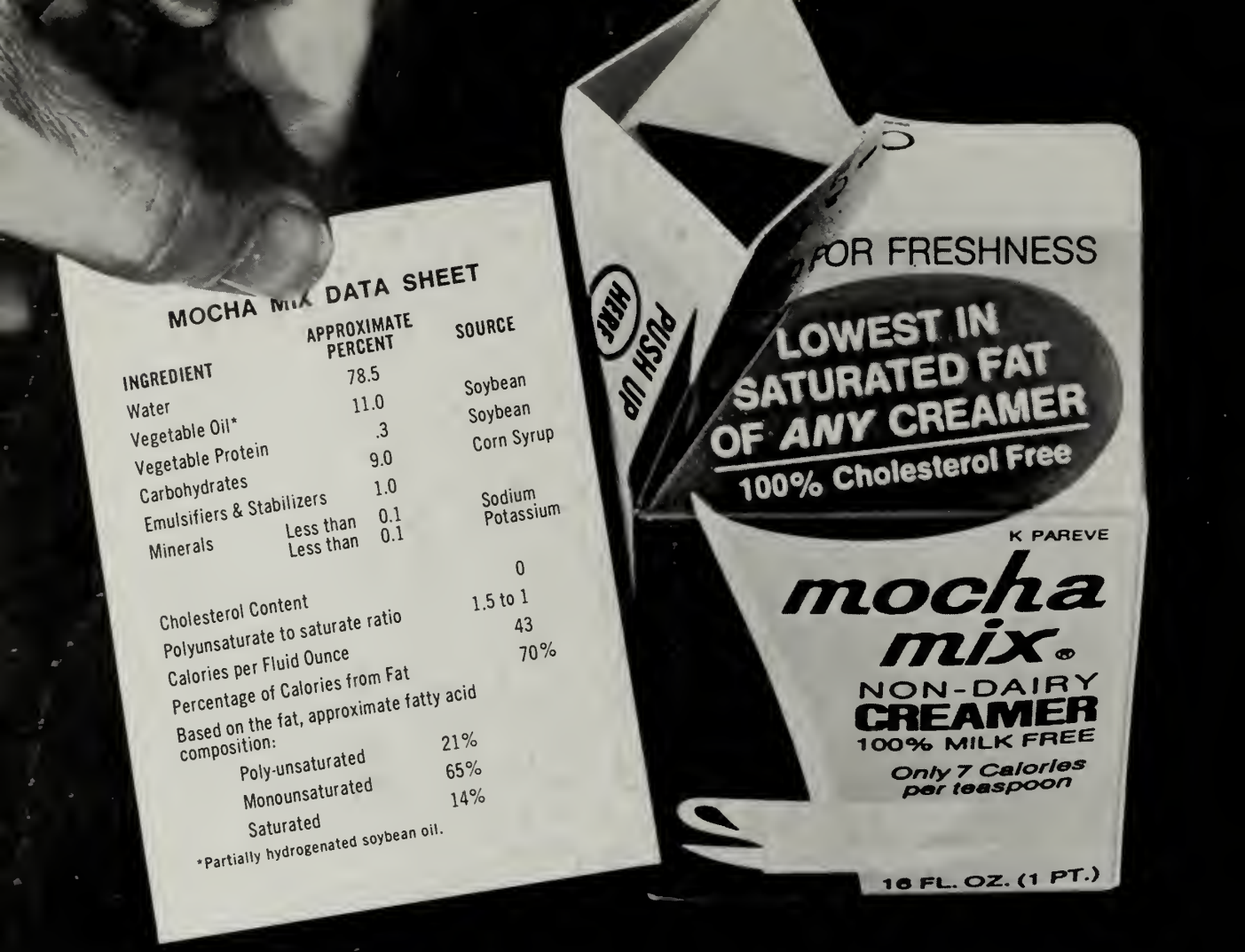

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THE WESTERN Journal of Medicine

VOLUME 121 • NUMBER 2 **AUGUST 1974**

91 *Gallium-67 Scans in the Diagnosis of Pyelonephritis*
WARREN O. KESSLER, MD, RUBEN F. GITTES, MD, SHELDON R. HURWITZ, MD, and JOSEPH P. GREEN, MD

94 *The Epidemiology of Influenza in California, 1968-1973*
JAMES CHIN, MD, ROBERT L. MAGOFFIN, MD, and EDWIN H. LENNETTE, MD, PhD

100 *Practical Aspects of Synovial Fluid Aspiration—The Approaches to Major Extremity Joints and Examination of the Aspirate* MARVIN H. MEYERS, MD

106 *The Use of Propoxyphene Napsylate in the Treatment of Heroin and Methadone Addiction*
DARYL S. INABA, PharmD, GEORGE R. GAY, MD, CRAIG A. WHITEHEAD, MD, JOHN NEWMEYER, PhD, and DAN BERGIN, BA

PSYCHIATRIC ROUNDS
112 *Anorexia Nervosa*
Case Presentation: J. HAMP ATKINSON, MD; Patient Interview: ROBERT NEMIROFF, MD;
Discussants: KITTY CLEVELAND, MD, and ALVIN ROBBINS, MD
University of California, San Diego, School of Medicine, San Diego Veterans Administration Hospital

MEDICAL STAFF CONFERENCE
123 *Wegener's Granulomatosis* Discussion by DAVID S. GULLION, MD

131 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Physical Medicine and Rehabilitation*

136 EDITORIALS • *Critical Masses in the Distribution of Health Care Services*
• *Gallium-67: Broad Spectrum Diagnostic?* • *New Hope for an Old Ill—Anorexia Nervosa*

CASE REPORTS
140 *Permanent Subcutaneous Gold Acupuncture Needles*
BARRY B. BEHRSTOCK, MD, and NICHOLAS L. PETRAKIS, MD

142 *Tick-Bite in Oregon: Paralysis in California*
RICHARD W. EMMONS, MD, F. MICHAEL BREWSTER, MD, and BERNARD C. NELSON, PhD

144 *Localization of a Parathyroid Adenoma by Thermography*
EUGENE C. WASSON III, LCDR, MC, USNR, JOHN L. SMITH, MD, and JAMES A. USSELMAN, MD

147 *Tricuspid Atresia and Aortic Origin of Right Pulmonary Artery in a Nine-Year-Old Girl*
LAWRENCE L. MENZER, MD, and MASATO TAKAHASHI, MD

150 LETTERS TO THE EDITOR

TRAUMA ROUNDS
153 *Assessment and Resuscitation of the Injured Patient* DONALD D. TRUNKEY, MD

GOVERNMENT AND MEDICINE
158 *The Guideposts in the RMP Odyssey* THE HON. CASPAR W. WEINBERGER

INFORMATION
163 *Occupational Health—Status of Governmental and Legal Control in California*

163 *Compensating Victims of Violent Crime* GILBERT GEIS, PhD

166 *In Memoriam*

168 *Book Reviews*

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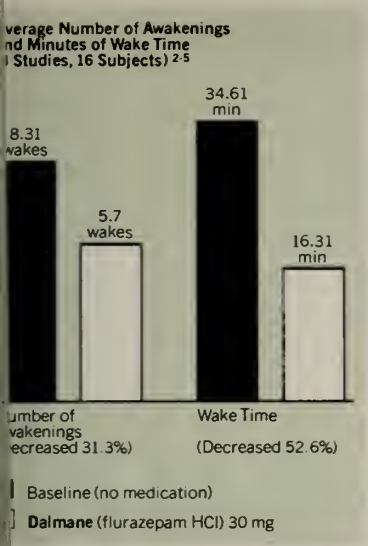

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utions: In elderly and debilitated, initial dosage should be ed to 15 mg to preclude oversedation, dizziness and/or ataxia. mbined with other drugs having hypnotic or CNS-depressant ts, consider potential additive effects. Employ usual precautions tients who are severely depressed, or with latent depression or dal tendencies. Periodic blood counts and liver and kidney ion tests are advised during repeated therapy. Observe usual utions in presence of impaired renal or hepatic function.

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ERENCES: 1. Kales J, *et al*: *Clin Pharmacol Ther 12*:691-697, Jul-Aug, 1971
racan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric ciation, Washington DC, May 3-7, 1971
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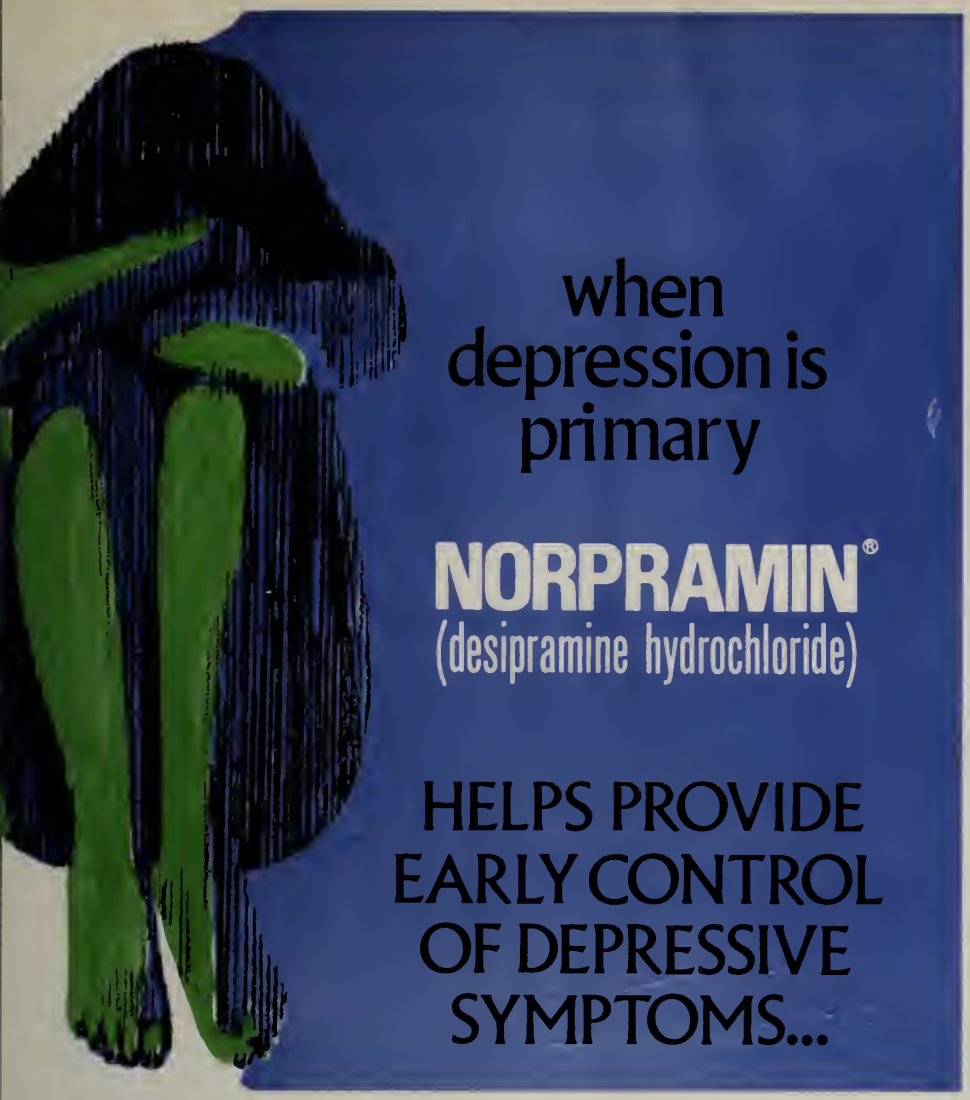

Anxiety is an invidious symptom. It feeds upon sickness, gnaws, grows and invades every cranny of psychic pathology adding intensity to torment. Anxiety as a symptom secondary to depression may be so dominant that it obscures the primary diagnosis. It may suggest treatment with tranquilizers which often help. But as the vampire of legend had to have a laurel stake driven through its heart to truly die, so anxiety secondary to depression will not cease to nibble and bite until an antidepressant eradicates the primary illness—and symptomatic anxiety starves.

IN BRIEF:

Indications: Norpramin® (desipramine hydrochloride) is indicated for the relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contraindications: Desipramine hydrochloride should not be given within two weeks of treatment with a monoamine oxidase inhibitor. Contraindications include the acute recovery period following myocardial infarction and hypersensitivity to the drug. Cross sensitivity with other dibenzazepines is a possibility.

Warnings: 1. Extreme caution should be used in patients: (a) with cardiovascular disease, (b) with a history of urinary retention or glaucoma, (c) with thyroid disease or those on thyroid medication, (d) with a history of seizure disorder. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. *Use in Pregnancy:* Safe use during pregnancy and lactation has not been established. 4. *Use in Children:* Norpramin® (desipramine hydrochloride) is not recommended for use in children. 5. This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Therefore, the patient should be cautioned accordingly.

Precautions: This drug should be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with drugs of this class. If possible, dispense in child-resistant containers. It should be kept out of reach of children. Reduce dosage, or alter treatment, if serious adverse effects occur. Norpramin® (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates and may cause exacerbation of phychosis in schizophrenic patients. Use cautiously with anticholinergic or sympathomimetic drugs. Response to alcoholic beverages may be exaggerated. In the concurrent administration of ECT and antidepressant drugs one should consider the possibility of increased risk relative to benefits. Discontinue as soon as possible prior to elective surgery because of possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is neutropenia.

Adverse Reactions: *Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. *Psychiatric:* confusional states (especially in the elderly), hallucinations, disorientation, delusions; anxiety, agitation; insomnia and nightmares; hypomania; exacerbation of phychosis. *Neurological:* paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, hypotonic bladder. *Allergic:* skin rash, petechiae, urticaria, itching, photosensitization, edema (of face and tongue or general), drug fever. *Hematologic:* agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue. *Endocrine:* gynecomastia; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels. *Other:* jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia. *Withdrawal Symptoms:* Though not indicative of addiction, abrupt cessation after prolonged therapy may produce nausea, headache and malaise.

Dosage and Administration: *The usual adult dose:* 50 mg. three times daily; increase if necessary after 7 to 10 days to maximum of 200 mg. daily. Dosages above 200 mg. per day are not recommended. *Maintenance:* At a lower dose adequate to maintain remission. *Adolescent and geriatric patient dose:* 25 to 50 mg. daily if necessary.

Overdosage: There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug. The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure and regulation of fluid- and acid-base balance are well known in most medical centers. If heart failure is imminent, digitalize promptly.

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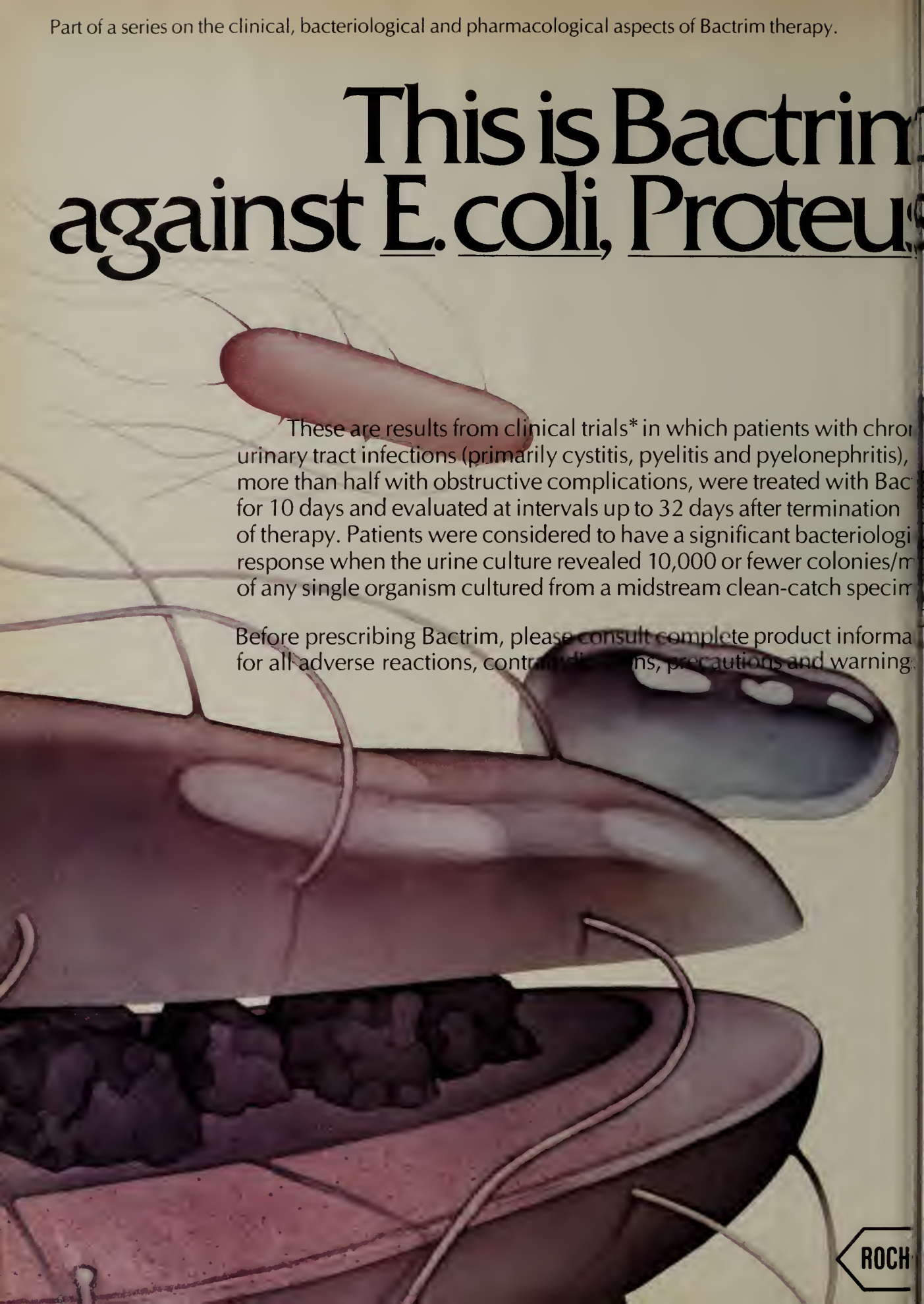

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	Excellent initial response* after 10 days of therapy	Impressive response maintained 32 days after termination of therapy
. coli infections	97.1% of 105 patients	73.1% of 93 patients
roteus spp. infections	81.1% of 37 patients	60.0% of 35 patients
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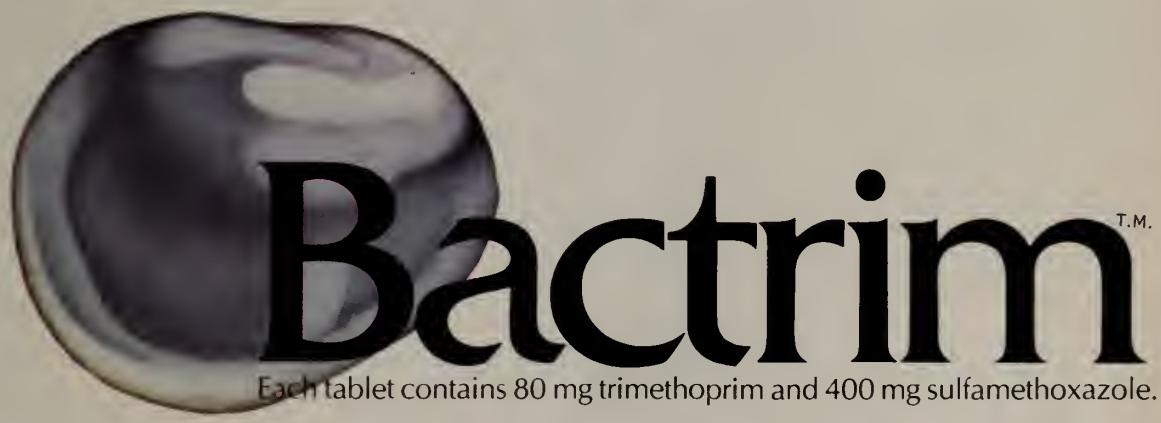

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

In cystitis, pyelonephritis and pyelitis diagnosed as chronic and due to susceptible urinary tract pathogens, usually E. coli, Klebsiella-Enterobacter and Proteus mirabilis.

Please see following page for summary of product information.

In cases of cystitis, pyelonephritis and pyelitis diagnosed as chronic*

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

- aggressive antibacterial activity
- interrupts essential metabolic process of susceptible organisms, usually E. coli, Klebsiella-Enterobacter, P. mirabilis, and, less frequently, indole-positive proteus species
- over 91% initial efficacy in clinical studies of patients with urinary tract infection diagnosed as chronic*
- impressive response even in cases with obstructive complications
- not recommended for children under 12, during pregnancy or the nursing period
- no loading dose; two tablets b.i.d. recommended for 10-14 days

*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species).

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in chronic and recurrent urinary tract infections.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia in elderly patients on diuretics, primarily thiazides. Sore throat, fever, pallor or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. Data are insufficient to recommend use in infants and children under 12.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, allergy or bronchial asthma; and in those with glucose-6-phosphate dehydrogenase deficiency, where hemolysis may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: Two tablets b.i.d. for 10 to 14 days. For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	2 tablets every 24 hours
Below 15	Use not recommended

Supplied: Tablets, each containing 80 mg trimethoprim and 400 m sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10.

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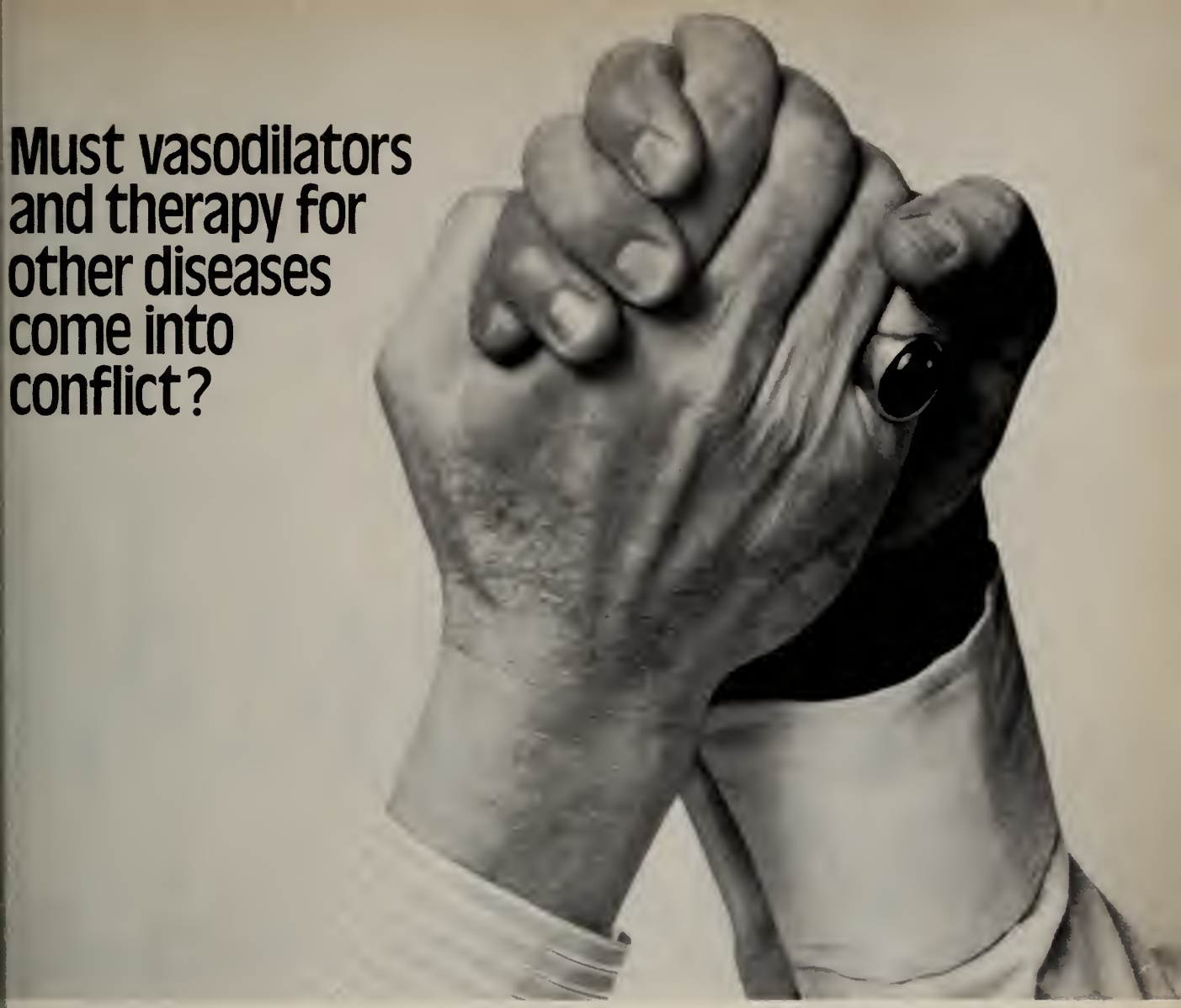
Must vasodilators and therapy for other diseases come into conflict?



not if the vasodilator is

VASODILAN®
(ISOXSUPRINE HCl)

the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

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Mead Johnson LABORATORIES

THE NATURAL WAY

For more than thirty years PREMARIN (Conjugated Estro Tablets, U.S.P.) has been prepared with natural equin estrogens exclusively—withou synthetic estrogen supplemen For more than thirty years it has provided the complete estro complex in the proportions fou in its natural source. And for m than thirty years PREMARIN enjoyed an unparalleled recor clinical efficacy and acceptanc

PREMARIN. The only estrog preparation available that cont natural estrogens exclusively an meets all U.S.P. specifications conjugated estrogens. Assuranc quality for you and your patie

PREMARIN . . . naturally

EF SUMMARY
F full prescribing information, see package ilar.)
EMARIN®
Conjugated Estrogens Tablets, U.S.P.)

dications: Based on a review of REMARIN Tablets by the National Acad-y of Sciences-National Research Council d/or other information, FDA has classified e indications for use as follows:
ective: As replacement therapy for nat-ally occurring or surgically induced estro-n deficiency states associated with: the cli-cteric, including the menopausal syndrome d postmenopause; senile vaginitis and aurosis vulvae, with or without pruritus.
robably" effective: For estrogen defi-ncy-induced osteoporosis, and only when ed in conjunction with other important erapeutic measures such as diet, calcium, ysiotherapy, and good general health-omoting measures. Final classification of s indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.
The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

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AND OF CONJUGATED ESTROGENS TABLETS, U.S.P.

CONTAINS ONLY NATURAL ESTROGENS ...NO SYNTHETICS OR SUPPLEMENTS

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STANFORD UNIVERSITY SCHOOL OF MEDICINE

OFFICE OF POSTGRADUATE MEDICAL EDUCATION

announces two interdepartmental five-day, comprehensive refresher courses

PRIMARY CARE OCTOBER 7-11, 1974

FOR FAMILY AND GENERAL PRACTITIONERS, GENERAL INTERNISTS AND GENERAL PEDIATRICIANS

Designed as a review of the principles and procedures involved in the management of patients with problems commonly encountered in primary care, the program includes a morning lecture series and afternoon elective problem-solving sessions, seminars, and demonstrations. Tuition for the course is $235, with registration required no later than October 4.

General lectures will cover the following topics: birth control, when and how to transfuse, motor vehicle injuries, prevention of heart attack, pre-CCU management of heart attack, rehabilitation after heart attack, urinary tract infections, nutritional anemia, management of rheumatoid and osteoarthritis, headache, depression, sleep disorders, new antibiotics, office management of diabetes, hypertension, comprehensive approach to primary care.

Elective sessions will include: **behavior modification:** obesity, smoking, alcoholism; **bones and joints:** neck and arm pain, low back and leg pain, bursitis and tendonitis, athletic injuries; **medical emergencies:** resuscitation, arrhythmias, drug ingestion, coma; **allergy:** hay fever, asthma, eczema and urticaria; **problem-oriented records:** the defined data base, construction of the problem list, workshop; **trauma:** hand injuries, face injuries, head and spine injuries, chest injuries; **dermatology:** contact dermatitis, bacterial and viral infections, fungal infections, dermatoses; **acid-base:** acidosis, alkalosis, mixed problems; **genetics and child health:** general review and cytogenetics, genetic counseling and prenatal diagnosis; immunization, school problems.

Faculty for this course will consist of thirty-five physicians of the Stanford University School of Medicine.

INTENSIVE CARE OCTOBER 28-NOVEMBER 1, 1974

FOR ALL PHYSICIANS INVOLVED IN THE CARE OF THE CRITICALLY ILL OR INJURED PATIENT

This course will review in detail the current status of management principles and procedures applicable to critically ill and critically injured persons. Topics of general interest will be covered in morning lectures, with the afternoon program offering a choice of problem-solving sessions and seminars and demonstrations in specialized topics. Thirty Stanford University School of Medicine faculty members will participate.

General lectures will cover: hemodynamic monitoring, antiarrhythmic drugs, surgery for ischemic heart disease, respiratory failure: pathophysiology-manifestations and management, the practical use of ventilators, clotting mechanisms, common bleeding problems: congenital-acquired, diabetic ketoacidosis and hyperosmolar coma, lactic acidosis, neurological emergencies, thromboembolism, drainage of the urinary tract.

Elective sessions will include: **EKG problems:** acute myocardial infarction, tachyarrhythmias, bradyarrhythmias, changes in severe illness; **blood gas and acid-base problems:** respiratory acidosis and alkalosis, metabolic acidosis, metabolic alkalosis, oxygen transport; **salt and water problems:** water, sodium, potassium, miscellaneous syndromes; **acute myocardial infarction**: cardiogenic shock, arrhythmias, emergency surgery, acute rehabilitation in CCU; **ICU methods:** resuscitation, protecting the brain after arrest, central venous pressure and arterial catheters, pacemakers; **trauma:** injuries to the face, injuries to the chest, injuries to the head and spine; **neonatal crises:** neonatal asphyxia, respiratory distress syndrome, sepsis, metabolic crises in the newborn; **ICU management problems:** use of blood components, acute renal failure, antibiotics in septic crises, hyperalimentation.

Tuition for this course is $225, with registration required no later than October 25. Early registration is advisable as this course has been oversubscribed in previous years.

Clip and mail to: OFFICE OF POSTGRADUATE MEDICAL EDUCATION
Stanford University School of Medicine, Room M121 • Stanford, California 94305

PRIMARY CARE **October 7-11, 1974**
Please enroll me ($235 check enclosed) _____ Please send brochure _____

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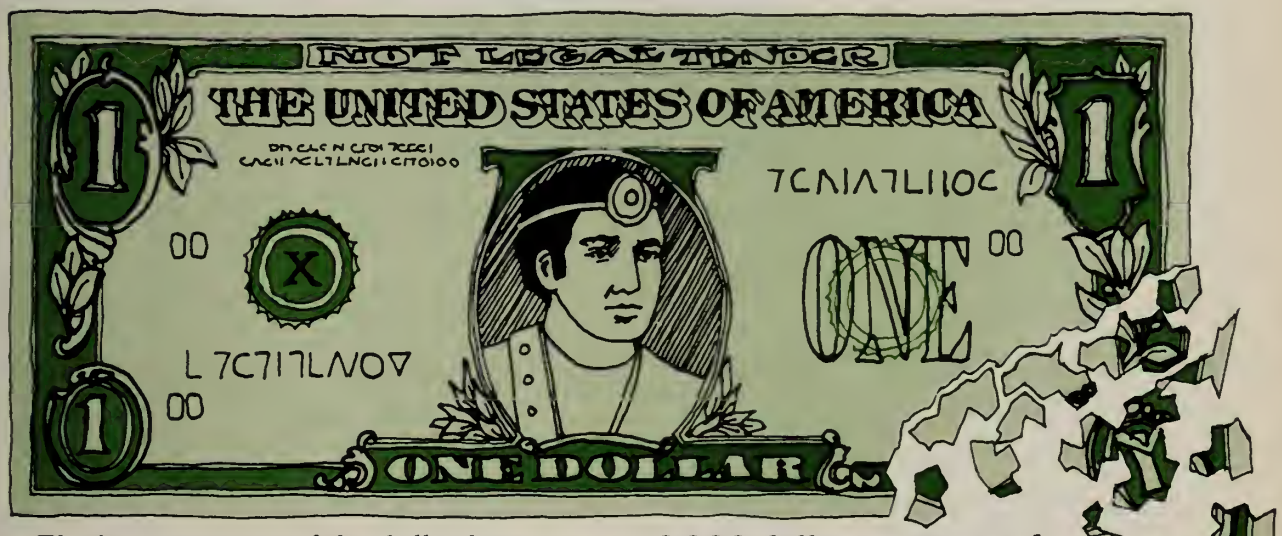
(Checks payable to STANFORD UNIVERSITY SCHOOL OF MEDICINE)

Has the value of your life deteriorated as much as the dollar?



The buying power of the dollar has depreciated by 17%* in the past two years. The value of your life, on the other hand, has increased immeasurably. You have a practice, a family and an estate. You may also have a $100,000 life insurance policy which, if purchased two years ago, will today buy only $83,000 worth of food, mortgage payments, clothes and tuition.

The CMA Special Term Life Insurance program helps solve the problem. You can now buy up to $50,000 coverage - depending on your age - at 1972 premium rates, when the program was first offered.

50,000 dollars guaranteed.

During August and September CMA members under age 50 are able to buy $50,000 coverage without evidence of insurability. All you need to do is list your beneficiaries and sign your name. For details, send us the completed coupon below.

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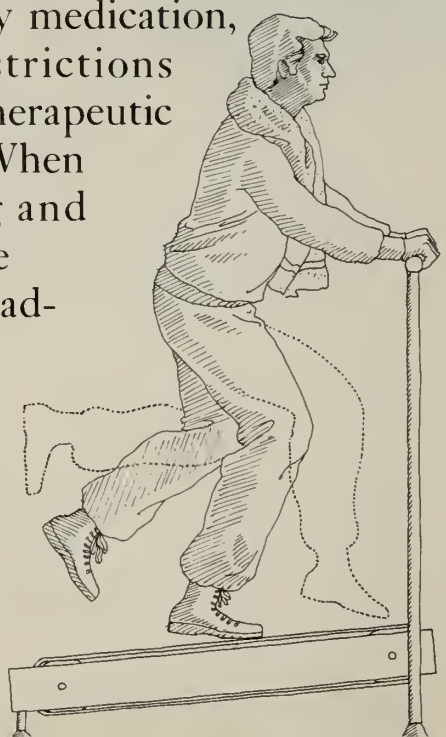
*Consumer Price Index, May '72 - May '74

Why add Librium® (chlordiazepoxide H to your cardiovascular regimen?

Excessive anxiety in susceptible patients can set in motion a chain of responses which add to the heart's work and thereby increase the possibility of cardiovascular complications. Furthermore, intense anxiety may interfere with effective medical management since some patients, in an attempt to deny their illness, may resist acceptance of necessary medication, dietary restrictions and other therapeutic directives. When counseling and reassurance alone are inadequate to relieve undue anxiety, junctive Librium (chlor azepoxide HCl) may beneficial.



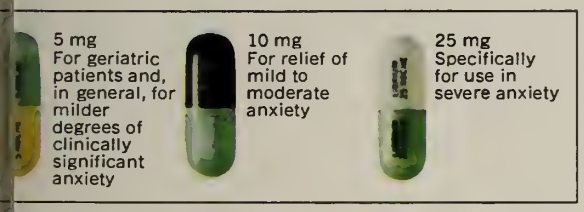
"Specific" for anxiety reduction... wide margin of safety

Librium is used as an adjunct primary cardiovascular medi tions, since it acts directly on central nervous system, reduc excessive anxiety and emotio tension. In so doing, Librium directly affects cardiovascu function.

Librium has a high degree antianxiety effectiveness with wide margin of safety. In pro dosage, Librium usually helps ca the overanxious patient with unduly interfering with men acuity or general performance. the elderly and debilitated, the tial dosage is 5 mg *b.i.d.* or less preclude ataxia or oversedation,

asing gradually as needed and
rated.

Librium is used concomitantly
h certain specific medications of
er classes of drugs, such as car-
glycosides, diuretics, antihy-
tensive agents, vasodilators and
coagulants. Although clinical
lies have not established a cause
effect relationship, physicians
uld be aware that variable effects
blood coagulation have been re-
ted very rarely in patients re-
ving oral anticoagulants and
rium. After anxiety has been
uced to tolerable levels, Librium
apy should be discontinued.


5 mg
For geriatric patients and, in general, for milder degrees of clinically significant anxiety
10 mg
For relief of mild to moderate anxiety
25 mg
Specifically for use in severe anxiety

r relief of excessive anxiety
unctive

ibrium® 10 mg
lordiazepoxide HCl)
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ROCHE

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Case history #5

Wayne's well-being comes first.

Wayne's being wel comes first.

For two weeks in 1972, Wayne Patton lay unconscious in an Oxnard hospital. Wayn a deputy sheriff for Ventura County, sustained serious injuries when his patrol car crashe on the way to a robbery scene. The accident left him partially paralyzed and caused disru tions in his ability to see, speak, and walk.

As soon as Wayne was sufficiently recovered, State Fund arranged for his transf to the Santa Barbara County Rehabilitation Center, where he was given extensive rehabi tation therapy. He made rapid progress toward recovery.

After three months of care, Wayne left the hospital. He was ready to rebuild his lif and State Fund was ready to help. After arranging for continued physical therapy and ou patient medical care, the State Fund staff enrolled him in Work, Inc., a sheltered worksh in Santa Barbara, and also arranged for his friends at the Sheriff's Department to drive hi to and from the workshop. In his first week at the shop, Wayne threw away his cane.

Although he was unable to take his old job back, State Fund worked hard to fi him a position in a related field. Today, Wayne Patton works full-time as an Air Pollutio Control Monitor.

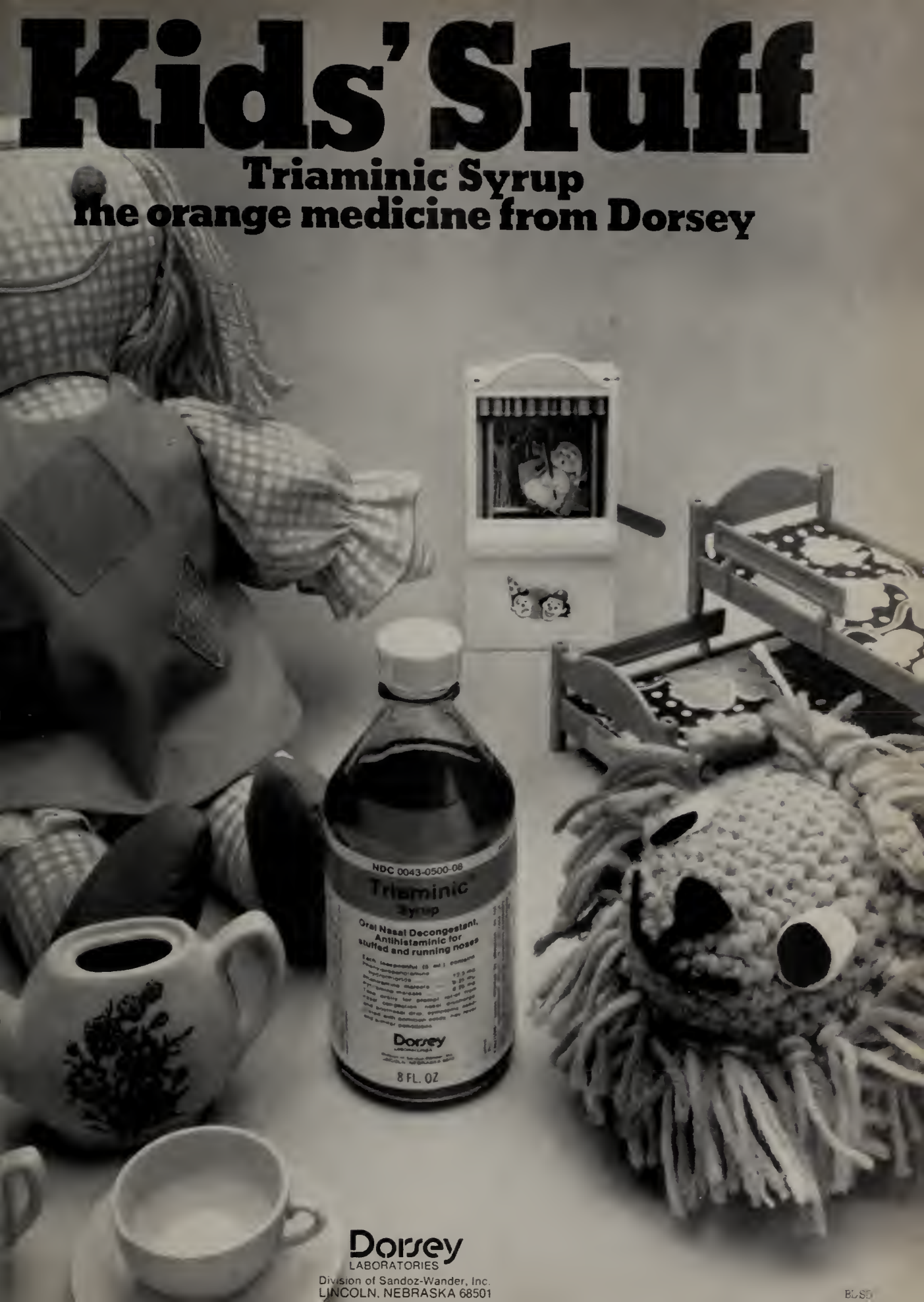
It took a lot of hard work and courage for Wayne to rebuild his life. Most of t credit belongs to him, but a lot of people helped: his wife, his doctors, his friends at t Sheriff's Department, and the people at State Fund.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND

Kids' Stuff

Triaminic Syrup
the orange medicine from Dorsey



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BLSD

IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin prepara should not be used. Antihistaminics appear beneficial in t ment of procaine reaction.

The use of antibiotics may result in overgrowth of nor ceptible organisms. Constant observation of the patient is es tial. If new infections due to bacteria or fungi appear du therapy, discontinue penicillin and take appropriate measur

If allergic reaction occurs, withdraw penicillin unless, in opinion of the physician, the condition being treated is threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected pri or secondary syphilis, perform proper diagnostic procedi including darkfield examinations. In all cases in which conc tant syphilis is suspected, perform monthly serological tests f least four months.

Adverse Reactions: (Penicillin has significant index of sitization) skin rashes, ranging from maculopapular eruptior exfoliative dermatitis; urticaria; serum sickness-like react including chills, fever, edema, arthralgia and prostration. Se and often fatal anaphylaxis has been reported. (See "Warning

As with other antisyphilitics, Jarisch-Herxheimer reaction been reported.

Administration and Dosage: Administer only by *deep muscular injection,* in upper outer quadrant of buttock. In in and small children, midlateral aspect of thigh may be prefer When doses are repeated, vary injection site. Before injec aspirate to be sure needle bevel is not in blood vessel. If b appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have creased susceptibility to penicillin, this resistance is relative absolute, and penicillin in large doses remains the drug of ch Physicians are cautioned not to use less than recomme doses.

Gonorrheal infections (uncomplicated)—Men or Women million units intramuscularly divided into at least two doses injected at different sites at one visit, together with 1 gram of probenecid, preferably given at least 30 minutes prior to injec

NOTE: Treatment of severe complications of gonorrhea sh be individualized using large amounts of short-acting peni Gonorrheal endocarditis should be treated intensively aqueous penicillin G. Prophylactic or epidemiologic treatmer gonorrhea (male and female) is accomplished with same t ment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, V real Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after the In the male, a gram-stained smear is adequate if positive; o wise, a culture specimen should be obtained from the ant urethra. In the female, culture specimens should be obta from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge pe 3 or more days following initial therapy and smear or cu remains positive. Follow-up treatment consists of 4.8 million u I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatme indicated if follow-up cervical or rectal cultures remain positiv *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic te syphilis at the time of diagnosis. Patients with gonorrhea also have syphilis should be given additional treatment ap priate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,40 units (4-cc. size) contains procaine penicillin G in a stab aqueous suspension with sodium citrate buffer, and as w/v ap imately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% vinylpyrrolidone, 0.01% propylparaben and 0.09% methylpara The multiple-dose 10-cc. vial contains per cc. 300,000 units caine penicillin G in a stabilized aqueous suspension with so citrate buffer and approximately 7 mg. lecithin, 2 mg. car methylcellulose, 3 mg. polyvinylpyrrolidone, 0.5 mg. sor monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalm 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

N SYPHILIS

JECTION

Bicillin® LONG-ACTING

STERILE BENZATHINE ENICILLIN G USPENSION) WYETH

yphilis is preferably treated with benzathine enicillin G, which is also the drug of choice r prophylaxis after exposure. Administra-n of 2.4 million units (1.2 million in each ttock) usually cures most cases of primary, condary and latent syphilis with negative inal fluid.

ndications: In treatment of infections due to penicillin nsitive microorganisms that are susceptible to the low and prolonged serum levels common to this particular dosage . Therapy should be guided by bacteriological studies (in-ing sensitivity tests) and by clinical response.

he following infections will usually respond to adequate ge of intramuscular benzathine penicillin G.—Venereal in-ions: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

ontraindications: Previous hypersensitivity reaction to any icillin.

Varnings: Serious and occasionally fatal hypersensitivity (ana-lactoid) reactions have been reported. Anaphylaxis is more uent following parenteral therapy but has occurred with oral icillins. These reactions are more apt to occur in individuals history of sensitivity to multiple allergens.

evere hypersensitivity reactions with cephalosporins have n well documented in patients with history of penicillin hyper-sitivity. Before penicillin therapy, carefully inquire into pre-s hypersensitivity to penicillins, cephalosporins and other gens. If allergic reaction occurs, discontinue drug and treat usual agents, e.g., pressor amines, antihistamines and corti-eroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

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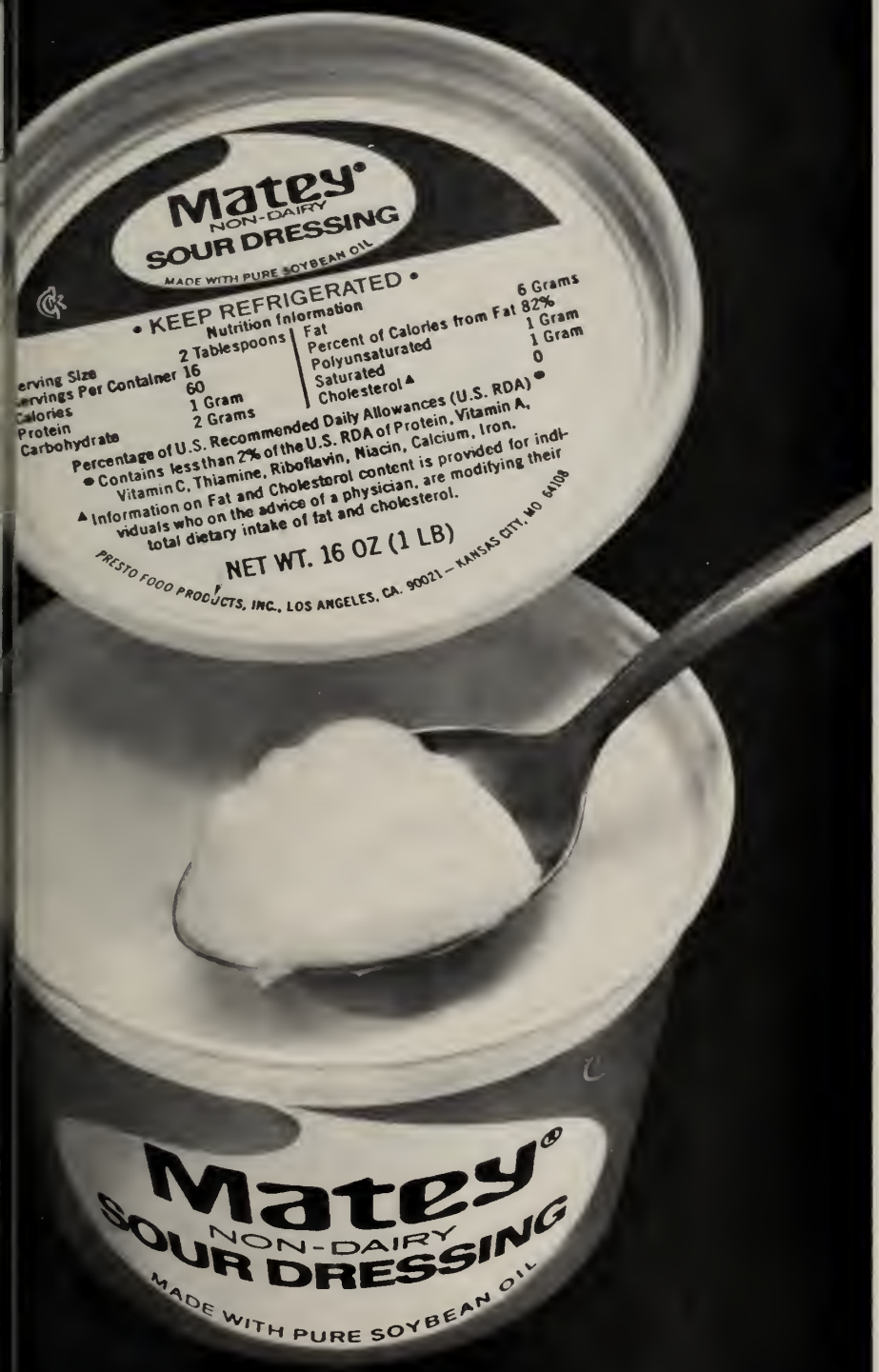

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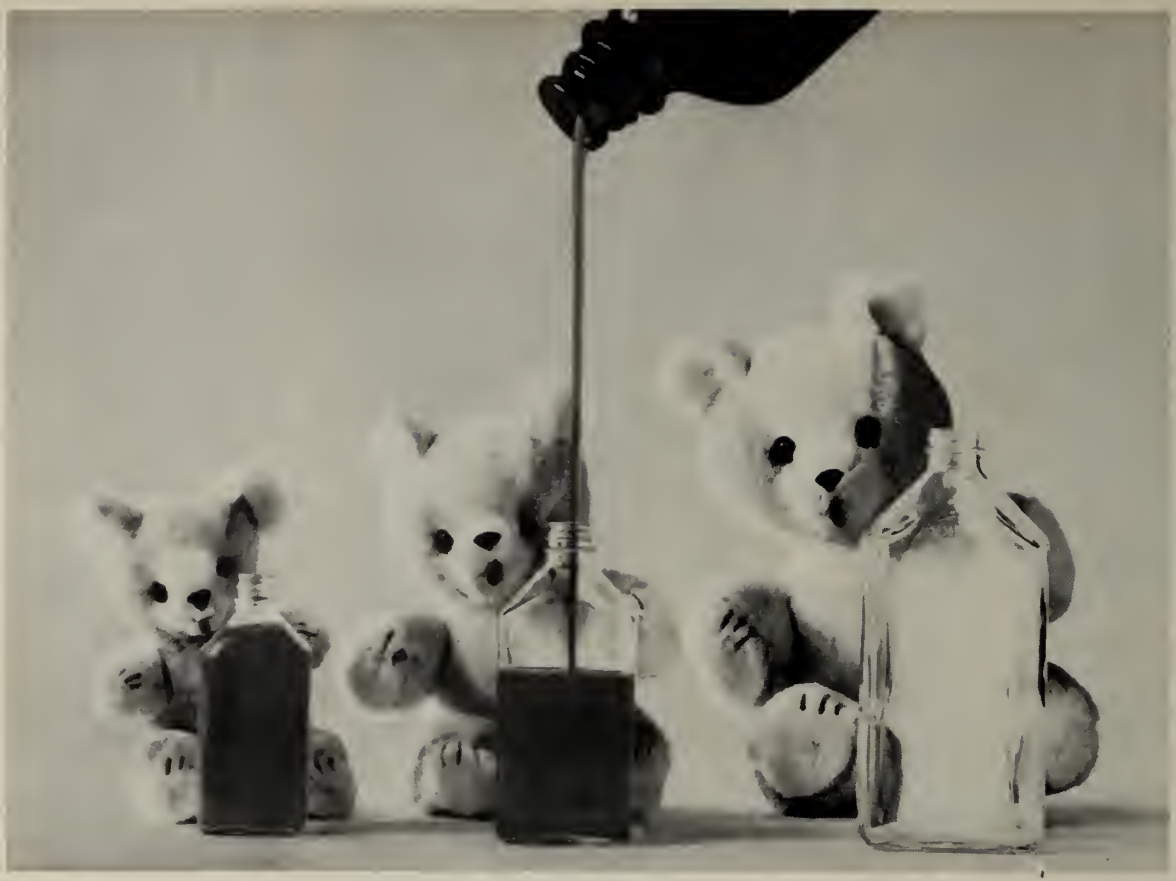

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THE WESTERN
Journal of Medicine

Gallium-67 Scans in the Diagnosis of Pyelonephritis

WARREN O. KESSLER, MD, RUBEN F. GITTES, MD, SHELDON R. HURWITZ, MD, and JOSEPH P. GREEN, MD, *San Diego*

Gallium-67 (^{67}Ga) citrate was administered intravenously (50 microcuries per kg of body weight) to patients in whom acute and chronic urinary tract infections were suspected. Scanning was done, using both the Anger-type scintillation camera and the rectilinear scanner, 24 to 78 hours after injection of the isotope.

The preliminary results imply that ^{67}Ga renal uptake is present in patients with pyelonephritis whether overt or silent, as well as in patients with ureterosigmoidostomies. However, ^{67}Ga renal uptake is not present in patients with radiographic evidence of chronic pyelonephritis without active infection and in patients without renal disease.

DISTINGUISHING UPPER FROM LOWER urinary tract infection has prognostic implications, may dictate the type and length of therapy, and may be a factor in determining the need for surgical intervention. The most reliable method for establishing the presence of upper tract infection is ureteral catheterization, but this is an invasive procedure and often requires the use of anesthesia and admitting the patient to hospital.

We report as a preliminary finding that selective renal uptake of gallium-67 (^{67}Ga) citrate occurs consistently in the presence of pyelonephritis, both overt and silent. Therefore, scintiphotography with this isotope may prove useful in differentiating between upper and lower tract infections.

From the Division of Urology, Department of Surgery, and Division of Nuclear Medicine, Department of Radiology, University of California, San Diego, School of Medicine.

Submitted January 7, 1974.

Reprint requests to R. F. Gittes, MD, Division of Urology, University Hospital of San Diego County, 225 West Dickinson Street, San Diego, CA 92103.

Methods

The usefulness of ^{67}Ga in searching for subphrenic abscesses has been reported previously.[1] After we noted the unexpected uptake of ^{67}Ga by the pyelonephritic kidneys of a patient being studied for a possible subphrenic abscess, a program was started in which 50 microcuries per kg of body weight of ^{67}Ga citrate was injected intravenously into patients in whom acute or chronic urinary tract infections were suspected.* Imaging was done at 24 to 78 hours after injection of the isotope, using both the Anger-type scintillation camera and the rectilinear scanner. Camera studies were done using the 184 KeV photopeak of ^{67}Ga with a 20 percent window and a medium energy diverging collimator. Normal uptake by the lumbar spine provided anatomic guidelines for interpretation of the scan. In the few instances where

*Gallium-67 citrate was provided by Mr. Harold Breslow of New England Nuclear, Billerica, Mass.

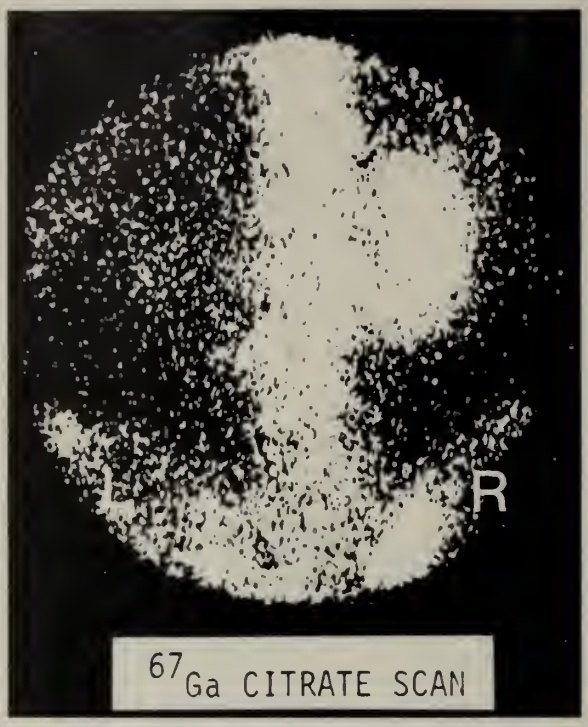

Figure 1.—Right renal uptake of gallium-67 in a patient with unilateral flank pain and pyelonephritis.

renal uptake was obscured by background activity, a kidney localizing dose of technetium 99m-DTPA was given.

Results

The results of ^{67}Ga isotope scans reviewed in this preliminary study are grouped as follows:

Retrospective Controls

Of all ^{67}Ga scans done as a tumor survey, 162 included the area of the kidneys. When reviewed for the purposes of the present study, there were only four patients with renal uptake of ^{67}Ga of these 162 patients. One of the four had hemochromatosis, and a second had chronic lymphocytic leukemia, but none had retrospective evidence of urinary tract infection. Therefore, in this series of incidental controls false positive results (such as uptake of ^{67}Ga in the absence of suspected pyelonephritis) were 2.5 percent.

Acute Pyelonephritis

This group was composed of 17 patients who all presented with overt signs of acute pyelonephritis. Renal uptake of ^{67}Ga was noted in all upon scanning. Sixteen of the 17 patient had urine cultures containing greater than 10^5 bacteria; the remaining patient had been treated with antibiotics 24 hours before obtaining the negative urine culture. Eleven of the patients had both unilateral flank pain and unilateral renal uptake of ^{67}Ga (Figure 1). Three patients with bilateral flank pain had bilateral isotope uptake, and three patients with unilateral flank pain had bilateral uptake with the greatest isotope concentration being localized to the side of the flank pain.

Silent Pyelonephritis

This group was composed of nine patients with pyuria and positive urine cultures without the typical picture of acute pyelonephritis. All of these patients had positive ^{67}Ga scans. In two of the patients, acute pyelonephritis was shown in biopsy specimens from the kidney and in three others positive results from Fairley washout tests suggested upper urinary tract infections.[2] Renal calculi were noted in a fifth patient (Figure 2), and the final three patients had a history of chronic urinary tract infections with at least two hospital admissions for sepsis.

Ureterosigmoidostomy

Four patients were studied in whom the drainage of urine had been diverted into the fecal stream by ureterosigmoidostomy. All of these patients had bilateral renal uptake of ^{67}Ga, although only one had overt acute pyelonephritis. In this patient, the ureterosigmoidostomy was converted to a bilateral ureteroileocutaneostomy because of repeated bouts of pyelonephritis and sepsis. His positive ^{67}Ga scan became negative after conversion of his urinary diversion.

Radiographic Pyelonephritis Only

Four patients with excretory urograms suggesting chronic pyelonephritis were studied. All four denied urinary tract infections for at least two months preceding the study, and the results of urine cultures were negative in all four. None of these patients had renal uptake of ^{67}Ga.

Discussion

Since Edwards and Hayes first reported the uptake of carrier-free ^{67}Ga in soft tissue tumors,[3] the isotope has become widely used in tumor evaluation[4] although the mechanism underlying the accumulation of ^{67}Ga has not been completely explained. Hayes et al.,[5] using autoradiography and electron microscopy, have demonstrated that ^{67}Ga accumulates in the lysosome-like organelles within cancer cells. Increased lysosomal activity, which is

Figure 2.—A 54-year-old man with nephrolithiasis shown on pyelogram (right). ^{99m}Tc-DTPA was used to localize the kidney as seen in the middle scintiphoto. On gallium-67 imaging, renal uptake is indicated by the double arrows (left).

characteristic of inflammatory cells, may also account for the affinity of inflammatory lesions for ^{67}Ga. It has also been postulated that the lower pH in tumor tissue resulting from anaerobic glycolysis allows for the formation of more stable gallium-proteinate complexes.[6] This mechanism may also pertain to abscesses where the pH decreases with the increasing age of the lesion.[7]

The preliminary results of the present study imply that selective renal uptake of ^{67}Ga is present in all patients with overt acute pyelonephritis. The test is also positive in asymptomatic patients in whom the diagnosis of acute pyelonephritis is otherwise suggested by the finding of significant bacteriuria in association with biopsy-proven acute pyelonephritis, positive results from a Fairley washout test, or the presence of renal calculi.

Renal scans with ^{67}Ga are also consistently positive in patients with ureterosigmoidostomies, a group of patients in whom the diagnosis of upper urinary tract infections can only be inferred. These results support the laboratory findings of Harbach et al. that all animals with ureterosigmoidostomies evidenced some degree of acute pyelonephritis histologically.[8]

Finally, ^{67}Ga renal scans are consistently negative in patients with radiographic signs of chronic pyelonephritis but without active urinary tract infections.

We may conclude that ^{67}Ga renal scans are eminently useful in the diagnosis of acute pyelonephritis whether overt or silent. However, before one can consider that a scan is positive on the basis of inflammatory disease, all tumors of the kidney including Hodgkins' disease and leukemic infiltrates, must be ruled out.

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Refer to: Chin J, Magoffin RL, Lennette EH: The epidemiology of influenza in California, 1968-1973. West J Med 121: 94-99, Aug 1974

The Epidemiology of Influenza in California, 1968-1973

JAMES CHIN, MD, ROBERT L. MAGOFFIN, MD, and EDWIN H. LENNETTE, MD, PhD, *Berkeley*

INFECTIONS AND ILLNESSES due to influenza viruses account for a large proportion of all acute respiratory diseases almost every year, and in addition there are epidemics of influenza at varying intervals. Influenza viruses, especially type A, periodically undergo pronounced changes in their antigenic composition. These antigenic variant strains of influenza viruses spread rapidly and cause widespread epidemics since the general population's immunity to these variants is low or absent. When these epidemics are in progress, most health departments are deluged with calls from medical groups, the general public and the news media regarding the presence, spread and severity of influenza. The Infectious Disease Section of the California State Department of Health has maintained an annual influenza surveillance program since 1957. This report considers the epidemiology of influenza in California based on findings of the surveillance program from 1968 to 1973, a period which spans the State's total experience with the Hong Kong variant (A/Hong Kong/1/68 [H_3N_2]) and its first year's experience with the English strain (A/England/42/72 [H_3-N_2]) of type A influenza virus.

From the Infectious Disease Section and the Viral and Rickettsial Disease Laboratory, State of California Department of Health, Berkeley.

Submitted March 7, 1974.

Reprint requests to: J. Chin, MD, Infectious Disease Section, California State Department of Health, 2151 Berkeley Way, Berkeley, CA 94704.

Materials and Methods

Surveillance System

A special surveillance system for the detection of influenza epidemics is operated each year in California through the joint efforts of the State Health Department and many cooperating local

Influenza is one of the most common acute febrile respiratory diseases in adults. Epidemics caused by influenza viruses occur every few years. When such epidemics are in progress, the medical community, the general public and the news media seek information regarding the presence, spread and severity of influenza. The methods and findings of the Influenza Surveillance System in California for the years 1968 through 1973 should be of interest generally. This period spans the total California experience with the type A Hong Kong variant (A/Hong Kong/1/68 [H_3N_2]), and the first appearance of the English strain of type A influenza virus (A/England/42/72 [H_3N_2]).

The surveillance of influenza during this period showed that there were major epidemics in Calfornia only during the state's first experience with the type A Hong Kong variant in 1968-69, and with the English strain in 1972-73. Problems and limitations in influenza surveillance do exist. Nonetheless, the major surveillance indices used (school absenteeism, laboratory data and deaths from pneumonia and influenza) are reliable and sensitive indicators of general trends of influenza virus activity. These indices are most useful in comparing the relative severity of influenza epidemics. However, since these indices usually lag several weeks behind the occurrence of disease, this lag must be considered in making estimates of current incidence trends based on these indices.

health departments. Several indices are used in this system.

• *School Absenteeism.* Procedures employed by the cooperating county health departments to determine school absenteeism vary. In some instances, one or two school districts are used. In others, schools throughout the county are requested to supply enrollment and absentee figures. Weekly absenteeism calculations are based on the number of school days during the week, the approximate enrollment in the school and the total number of students absent per day during the week.

• *Pneumonia and Influenza Deaths from Selected California Cities.* A total of 11 California cities, representing about 30 percent of the state's population, provides reports of pneumonia and influenza (P and I) deaths. At the beginning of each influenza season (October through May), a normal or expected incidence curve of P and I deaths is calculated and charted.[1] This curve represents a smooth moving average of the P and I deaths reported by the 11 cities during the past five years, adjusted for population increase in those cities. An epidemic threshold (1.645 standard deviations above the normal incidence curve) is also plotted on the chart to provide a guide for the detection of significant increases in P and I deaths above those expected. During the influenza season, weekly P and I deaths are graphed as the data are received.

• *Laboratory Tests for Influenza on Selected Specimens Submitted to the State Viral and Rickettsial Diseases Laboratory and Special Studies in Selected Population Groups.* Serologic studies consist of Complement Fixation (CF) and Hemagglutination Inhibition (HI) antibody tests on routinely collected sera or blood or on whole blood collected

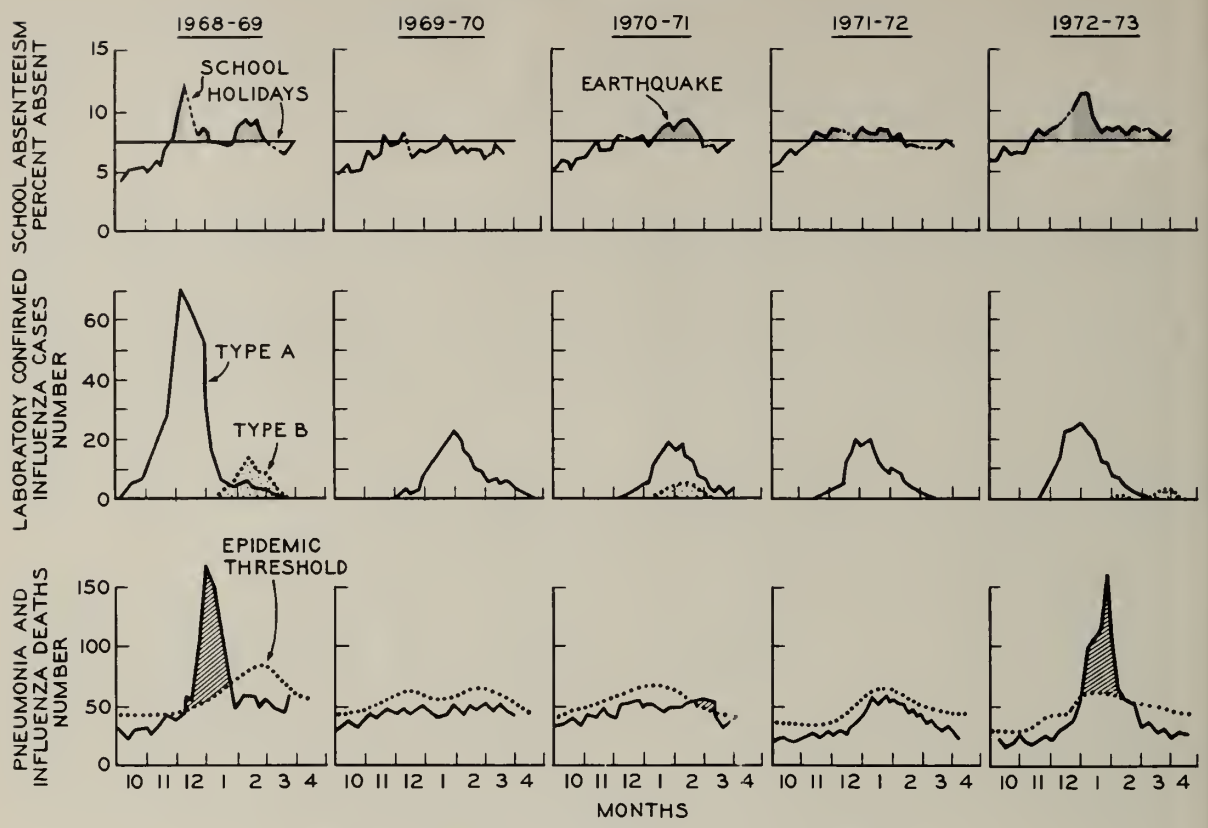

Chart 1.—Influenza surveillance indices used in California

on filter paper discs.[2] Virus isolation, when done, routinely is in tissue culture and in embryonated eggs. Standard methods are used for all tests.[3]

Results

Influenza Surveillance Indices

Chart 1 presents the three main influenza surveillance indices (school absenteeism, virus laboratory test results and excessively large numbers of deaths from pneumonia and influenza) for the influenza seasons in 1968 through 1973. It can be seen readily that, although influenza virus activity can be documented for all of these seasons, major epidemics in California were encountered only during the State's first experience with the Hong Kong variant in 1968-69, and with the English strain in 1972-73. The agreement observed among the indices used is relatively good, especially between school absenteeism and deaths from pneumonia and influenza. However, a lag of about a month is noted for the P and I death index, compared with the other two indices.

Type B influenza virus activity was recorded both shortly after the major outbreak of type A "Asian influenza" in the 1968-69 season and concurrent with the Asian strain during the 1970-71 season. In each instance, it was reflected by a pronounced increase in school absenteeism rates. The peak of the influenza season in California, as shown by the indices, is usually reached around February, although the 1968-69 and the 1972-73 seasons were a month or two early.

Table 1 presents the serologic results for the common respiratory agents of adults obtained by routine testing of blood specimens obtained from patients in the acute and convalescent phases and submitted to the State Viral and Rickettsial Diseases Laboratory. It can be seen that influenza infections even during nonepidemic years accounted for most of the documented respiratory illnesses during the respiratory disease season.

Outbreak at Needles, California

Antibody titers in patients who were in the convalescent phase of the syndrome in question, to influenza viruses, adenovirus and Mycoplasma pneumoniae are presented in Table 2. In at least half of the 24 patients, some demonstrable antibody to all of these agents was noted. However, when levels of antibody at a titer of 1:32 or

TABLE 1.—*Results of Complement Fixation Tests for Influenza Antibody on Paired Serum Specimens Submitted to the California State Viral and Rickettsial Diseases Laboratory from Patients with Respiratory Illnesses—October through May*

Respiratory Disease Season	Total Number Tested	Tests with Four-fold or Greater Antibody Rise to: Influenza A		Influenza B		Adenovirus		Mycoplasma pneumoniae	
		No.	Percent	No.	Percent	No.	Percent	No.	Percent
1968-69	2,590	562	21.7	87	3.4	NA	..	NA	..
1969-70	1,814	201	11.1	1	0.1	21	1.2	92	5.1
1970-71	1,792	140	7.8	30	1.7	24	1.3	64	3.6
1971-72	1,467	147	10.0	0	0.0	26	1.8	69	4.7
1972-73	1,879	193	10.3	18	1.0	35	1.7	115	6.1

NA—Not Available

TABLE 2—*Results of Serologic Tests on Sera Obtained from 24 Patients Two Weeks or More After Onset of Acute Influenza-Like Symptoms—Needles, California, November, 1968*

Serologic Test	CF Influenza Type A	HI Influenza Type A	CF Adenovirus	CF Mycoplasma pneumoniae
Number with antibody ≥ 1:8	18	22	12	13
Percent	75.0	91.7	50.0	54.1
Number with antibody ≥ 1:32	13	17	1	1
Percent	54.2	70.1	4.2	4.2

TABLE 3—*Titers of Hemagglutination-Inhibiting (HI) Antibody to the A/Hong Kong/1/68 (N_2H_3) Influenza Virus in Primary School Children from Southern California, April-May 1969*

Grade	Ages	Number Tested	No. with HI Antibody Titer ≥ 1:32	Percent
2nd	7- 8 yrs.	700	149	21.3
4th	9-10 yrs.	810	200	24.7
6th	11-12 yrs.	855	231	27.0
Totals		2,365	580	24.5

greater were considered, the results were strongly indicative of influenza virus type A as being the agent causing the outbreak. This impression was confirmed by isolation of a type A virus with characteristics of the A/Hong Kong/1/68 (H_3N_2) from one of the three throat swab specimens collected from patients in this outbreak.

Serologic Survey

Results of the serologic survey of primary school children in five Southern California cities conducted several months after the 1968-69 Hong Kong influenza epidemic, are presented in Table 3. Essentially, uniform rates of infection were found in each of the areas studied. The percentage of children with an HI antibody titer of ≥1:32 to the Hong Kong virus appeared to increase slightly with age and ranged from 21 to 27 percent.

Discussion

Every year during the respiratory disease season, a multitude of infectious disease agents causes an increase in the incidence of respiratory symptoms in the general population. This annual seasonal increase is expected and, in one sense, might be termed an annual epidemic. However, the increased incidence of respiratory illnesses during the respiratory disease season is not considered unusual or disruptive to normal community functions. Society has, for the most part, adjusted to this annual situation. While some cases of influenza occur every year, more extensive and widespread outbreaks of influenza type A tend to occur every two to three years, and limited outbreaks of influenza type B tend to occur at five to six year intervals. Influenza outbreaks usually overshadow the existing pattern of respiratory disease. Furthermore they are likely to cause greater disruption of community activities than do outbreaks of other respiratory diseases.

The clinical identification of influenza is difficult in individual sporadic cases since similar clinical symptoms can be caused by other viral agents for which accurate differential diagnosis is dependent on laboratory tests. The general use of the term "flu" also causes considerable confusion when the incidence of influenza is being assessed. Influenza is commonly referred to as the "flu" but this term is also widely applied to syndromes in which nausea, vomiting and diarrhea are predominant symptoms. Gastrointestinal symptoms are usually *not* the predominant ones associated with influenza virus infections, and such clinical syndromes usually do not warrant a clinical diagnosis of influenza. The clinical syndrome associated with influenza A has been relatively consistent over the past several decades. Typically the symptoms encountered are fever, chills, mal-

aise, headache, myalgia and general weakness. Although upper respiratory symptoms consisting of nasal irritation and a dry nonproductive cough may be noted early, the constitutional symptoms generally are more pronounced.

Aside from the difficulty of clinical diagnosis, surveillance of influenza is hampered by the fact that individual case reports of influenza are not required from physicians and hospitals. Clearly, such reports would have little worth after an epidemic is under way. However, suspected initial cases, outbreaks or unusual occurrences of influenza should be reported to the local health officer when recognized. The surveillance of influenza, therefore, depends on the development of indices which can be used to detect its appearance and monitor its extent. However, it has to be understood that the indices used to monitor influenza have expected or normal values which reflect the average incidence of respiratory disease from many causes including influenza. When the normal values are exceeded for absenteeism or for recorded pneumonia or influenza deaths, this indicates a general trend of increased illness, only part of which may be due to influenza. These indices are useful indicators of influenza activity in the general population. However, it is not possible to equate actual numbers of absentees or deaths from these indices with cases of influenza, since the relative contribution of influenza to these indices is not precisely defined.

School absenteeism is one of the earliest and best indicators of influenza activity, but this index has to be interpreted with some caution in any particular area. For example, high school absenteeism rates in some Northern California counties increased by as much as 30 to 40 percent at the beginning of the fall duck hunting season. Natural disasters, such as local floods or earthquakes, also significantly elevate this index. School recesses during Christmas and Easter make this index useless for these periods.

Experience in California with the Hong Kong variant of the Asian influenza virus began in the summer of 1968. Reports were received by the State Health Department in late July, 1968, of an outbreak of Asian influenza in Hong Kong. The virus isolated in this outbreak was found to vary significantly from previous Asian influenza virus strains. Because of this difference, extensive outbreaks due to the Hong Kong virus were expected throughout the world. Isolated cases of influenza due to the Hong Kong virus in California were confirmed by the State Viral and Rickettsial Diseases Laboratory starting in August 1968. As in 1957, when the first Asian (A2) influenza virus was first recognized, repeated seedings of the virus into the United States were confirmed for several months before widespread outbreaks throughout the nation.[4]

The first confirmed outbreak in the United States during the 1968-69 influenza season was early in September, 1968, in San Diego.[5] It involved 22 drill instructors at a military facility. The first outbreak in a civilian population of "Hong Kong flu" in the United States was confirmed in Needles, California, a town near the Arizona border.[6] Starting in late September, a high incidence of an influenza-like syndrome was noted mainly in high school students although many family groups were also affected. A rapid investigation was made by epidemiologists from the California Department of Health and the cause of this outbreak was attributed to the Hong Kong variant when the results of testing blood specimens from convalescent patients showed high antibody titers to this agent. This impression was confirmed by isolation of the virus from an acutely ill patient in Needles.

In December, 1968, a consistently rising incidence of school and industrial absenteeism was noted in Los Angeles.[7] The incidence of influenza cases peaked in the southern counties of the state by the end of December, 1968, or early January, 1969. In the northern and central counties influenza virus activity was intense but somewhat spotty and was never noted to be as widespread throughout the general population as was reported in the southern counties.

After an extensive epidemic of influenza, such as experienced during the 1968-69 season, it might be expected that the majority of children would have antibodies to the specific virus involved. The results of the serologic survey of school children in Southern California shortly after the epidemic showed that only about a quarter of the children had evidence of infection with this virus. These results are consistent with a serologic survey conducted in Panama,[8] where an infection rate of 23 percent in children aged 3 to 12 years was noted after the epidemic of the Hong Kong variant. The infection rate increased gradually with age, exceeding 50 percent in adults. From these results it can be concluded that a relatively large proportion of the population, particularly children, is still susceptible to a new influenza variant even

after a widespread outbreak. Thus, in subsequent years, extensive disease due to this virus may still occur. In California, there was a significant number of infections due to the Hong Kong variant in each of the first three years after the virus appeared. During the 1972-73 season, no isolates of the Hong Kong variant virus were made and all of the type A influenza occurring in California was due to the English strain of type A influenza.

The experience with type A influenza in California is similar to that encountered throughout the United States during the same years, with the exception of the 1971-72 influenza season. No major outbreak of influenza in California was noted from 1969 to 1972. However, a large outbreak of influenza due to the Hong Kong variant was recorded during 1971-72 for most areas in the United States. It is not clear why California was spared during the 1971-72 season. The national press, which was greatly influenced by the incidence of the illness on the east coast of the country, gave considerable attention to the 1971-72 influenza season. With frequently occurring respiratory-influenza-like syndromes, plus the widespread publicity regarding the "national epidemic," it was impossible to convince the news media and the public that there was not an extensive epidemic of influenza in California.

If past epidemiologic patterns of influenza continue, there will not be an extensive influenza epidemic in California until the next major variant of type A influenza virus appears. Between the major epidemic periods, physicians should consider administering influenza vaccine routinely to patients considered at high risk to complications of influenza. These patients include the elderly, and those with chronic medical problems.[9] With the advent of highly purified and potent influenza vaccine, reactions to it are not as troublesome as they once were and consideration should be given to using it more extensively. However, when vaccine to the circulating influenza virus strain is in short supply, priorities have to be developed. At such times, the available influenza vaccine should be restricted to those individuals considered at high risk to complications to influenza.

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Practical Aspects of Synovial Fluid Aspiration

The Approaches to Major Extremity Joints and Examination of the Aspirate

MARVIN H. MEYERS, MD, *Los Angeles*

Use of a few simple office laboratory procedures can provide accurate diagnosis of several forms of common diseases of joints. The average physician can discover unsuspected joint disease in this way, thereby avoiding expensive laboratory tests and delay in making the diagnosis. An adequate history and physical examination are needed in conjunction with analysis of fluid aspirated from the joint.

THERE ARE SEVERAL relatively simple laboratory procedures which can facilitate a rapid and accurate diagnosis of various forms of joint disease. The necessity for simple testing of joint effusion at the time the specimen is taken is not universally appreciated. The physician can discover unsuspected joint disease by this technique. Thus, much time, effort and expense can be saved in the diagnosis of monarticular arthritis. The technique of arthrocentesis of the various extremity joints has proved to be the best route to the joint involved.

It should be emphasized that synovial fluid aspiration and analysis cannot supplant a thorough history and physical examination. In most instances the simple tests discussed here will be sufficient, in conjunction with an adequate history and physical examination, to make an accurate diagnosis. However, occasions will arise when more complicated specific tests will be required, in addition, to establish a diagnosis.

From the Orthopedic Section, Department of Surgery, University of Southern California School of Medicine, Los Angeles.

Submitted December 17, 1973.

Reprint requests to: M. H. Meyers, MD, Section of Orthopedic Surgery, University of Southern California School of Medicine, 1200 North State Street, Box 404, Los Angeles, CA 90033.

Anatomy and Physiology

A diarthroidal joint consists of two articular hyaline cartilaginous surfaces with a capsule connecting them. The inner joint surfaces are lined by a connective tissue structure called synovial membrane. The cartilaginous surfaces are not covered by synovium.

Hyaline cartilage is avascular and contains few if any lymph vessels and nerves. The synovial membrane, on the other hand, is vascular and contains nervous tissue elements. The cartilage is resilient. This property along with lubrication by the joint fluid permits the articular cartilage to act as a cushion.

Respiration of the cartilage is practically nonexistent, whereas respiration of the synovial mem-

brane is similar to that of other tissues. The hyaline cartilage has minimal regenerative power, whereas the synovial membrane regenerates readily.

The nutrition of joint cartilage is probably derived from the synovial fluid and from vessels beneath the subchondral plate. There is some evidence that pressure exerted on cartilage forces nutrients into it.[2]

Inflammatory processes, such as rheumatoid arthritis, cause an increase in the protein content of synovial fluid. There follows an increased connective tissue growth with formation of scar tissue. The scar tissue, or pannus, may suffocate the cartilage by interfering with its nutrition. Scarring can lead to fibrous ankylosis and, if cartilage is completely destroyed, to bony ankylosis as well. Hyaluronic acid, the mucopolysaccharide loosely bound to protein that constitutes mucin, is completely depolymerized and is produced in larger amounts with an increased amount of edema fluid. A cellular reaction is produced depending upon the type of stimulus. At present no specific causitive agent has been found.

The most common pyogenic organisms causing inflammatory reaction are gonnococcus, meningococcus, pneumonococcus, staphylococcus and streptococcus. Cartilage may undergo chondrolysis by enzymes from lysosomes that are stimulated by kinius produced by these organisms. The glycolytic characteristic of these organisms is responsible for the much lower sugar content found in the synovial fluid from pyogenic joints than is found in the serum.

Degenerative joint disease results in continued wear and tear, causing fibrillation of the cartilage. The ground substance disappears and the collagen fibers are seen through the ground substance. There follows an active growth of primitive cells where the cartilage blends with transitional tissue of the synovium, and secondarily a metaplasia of cartilage and bone leads to bony spurs. The cartilage is lost and the exposed bone then becomes eburnated.

Normal Synovial fluid

Synovial fluid normally exists in small amounts. The fluid is clear, pale yellow and viscous. It does not clot spontaneously. Normal fluid contains:[4]

- Electrolytes
- Small molecular non-electrolytes such as uric acid, glucose, and non-protein nitrogen
- Albumin and globulins
- Mucin
- Blood cells
- Other miscellaneous substances such as enzymes, cartilage debris.

Electrolytes and small molecular non-electrolytes readily diffuse through the synovial membrane and follow the Donnan equilibrium.

Albumins and globulins are large molecular proteins which permeate capillary walls with difficulty and are, therefore, found in lower concentration in the synovial fluid than in plasma. The protein content is lower than in the serum. Thus, materials bound to proteins are found in significantly smaller amounts in the joint fluid. There is no fibrinogen in normal synovial fluid.

Mucin is a glycoprotein which consists of hyaluronic acid bound to protein.[1] Hyaluronic acid is probably produced by the living cells. It is denatured in the presence of local inflammation and by mechanical factors. Mucin causes the viscosity of synovial fluid and precipitates as a thick, tight, ropy curd with a clear supernatant upon the addition of acetic acid.

Normal synovial fluid contains from 13 to 180 free cells per cu mm.[1] Polymorphonucleated leukocytes account for about 25 percent of this total. The remainder is composed of mononucleated cells and a few synovial cells.[5] There are no red blood cells.

Most chemotherapeutic agents given systemically attain a concentration in synovial fluid only slightly less than that in plasma. Substances injected into a synovial joint readily diffuse into the surrounding extracellular spaces and capillaries if they are of small or moderate molecular size. Large molecular substances and particulate matter (such as red blood cells, bacteria) are removed slowly by lymphatics and phagocytosis.[4]

General Considerations in Joint Paracentesis

The optimum site for paracentesis of a joint is the anterior aspect of most extremity joints except the wrist, elbow and digits. The exceptions are approached from the posterior aspect. The synovial pouch is closest to the skin and located farthest from major nerves, arteries and veins.

Great care must be taken in performing the various steps during aspiration lest injury be done to important structures in close relationship to the joint being aspirated or infection be intro-

duced, possibly leading to severe pyoarthrosis and osteomyelitis.

The skin must be sterilized before a needle is inserted and all instruments must be sterile. The skin is prepared by scrubbing with an antibacterial detergent for 5 minutes, and the area then is wiped dry with sterile gauze and painted over with an antiseptic agent.

Materials

The materials that must be at hand are:

- A small tray
- Detergent or skin antiseptic
- Alcohol sponge
- 1 percent solution of lidocaine (Xylocaine®)
- Needle, 24 gauge, 1½ inches long
- Needle, 18 gauge, 2 inches long
- Sterile syringe, 2 ml
- Sterile syringe, 30 ml
- Collecting tubes—
  - One sterile oxalated
  - One sterile non-oxalated
  - Two plain

Paracentesis

The area is covered with a sterile drape that has an opening large enough to expose a small area for insertion of the needle. Use of a mask and sterile gloves also are prophylactic measures that should be taken. The portion of the needle which enters the joint is not to be touched. The skin and deeper tissues down to the synovial membrane are infiltrated with 1 or 2 ml of 1 percent Xylocaine. A 30 ml syringe and an 18-gauge needle approximately three inches long is preferred for aspiration of the joint. For digital joints a 22-gauge needle is used. When aspiration is not necessary, a smaller syringe and a long 24-gauge needle is used for the injection of medication into the joint. If an injection is to be done, it is better to discard the needle used to withdraw from the bottle the material to be injected, and affix another one to the syringe for penetration into the joint. (Since the joint usually is aspirated before injection, one can aspirate the joint, then disengage the syringe from the needle already in the joint and affix to it the syringe containing the medication.) This procedure avoids the hazard that small amounts of the drug which might cling to the outside of the needle could be trapped in the soft tissue and cause inflammatory reaction.

The aspirate should be collected in several tubes for the various diagnostic procedures: Five ml of aspirate is put into a sterile oxalated tube and another 5 ml into a non-oxalated sterile tube; a third specimen is put into a plain tube, and 1 to 2 ml goes into a fourth tube for the mucin qualitative test.

Insertion of the needle into a distended capsule is not difficult. It is slightly more difficult to penetrate the joint when the capsule is not distended. The end of the needle, once in the joint, may be obstructed by small particles of cartilage, cellular debris or the fat pad in the knee. The removal of most of the effusion is expedited by wrapping the joint, except for the site of the aspiration, with an elastic bandage. This step is not essential, however.

Once the needle has entered the joint, it should be moved very cautiously lest damage be done to the articular cartilage. If there is uncertainty as to whether the needle is in the joint, an x-ray film will clarify its position. Where available, using an image intensifier fluoroscopy screen can be helpful. Barbotage of saline solution into the joint and then back into the syringe will occur readily if the needle is in the joint. Also, radiopaque dye (Hypaque®) can be inserted and x-ray films taken to make sure the needle actually is within the joint space. Refer to Figures 1 through 8.

Analysis of Synovial Fluid

The appearance of the synovial fluid is noted. The viscosity can be tested by putting a drop of fluid between the thumb and middle finger and gently separating the fingers. Normal fluid is quite viscous. An examiner can become adept at qualitatively determining normal viscosity after performing the test several times. The viscosity changes from normal to a less viscid consistency as one proceeds down the table of pathological entities (Table 1) to a point where there is very little viscosity in fluid from a septic joint, the adherence of the gloved fingers with a drop of septic synovial fluid between them being almost the same as with a drop of water.

Fluid is collected in an oxalated tube and is sent to the laboratory for a cell count and differential smear. Aspirated fluid (2 to 5 ml) is placed in a sterile tube and is sent to the laboratory for culture and a Gram-stain smear. Fluid is collected in a third tube and is sent to the laboratory for glucose determination. The fourth tube is used for a mucin clot test which is done almost im-

The illustrations depict the topographical anatomical sites for paracentesis of each extremity joint. Proper sterile precautions are described in the text. (As the pictures are for illustration only, the hands are shown bare rather than gloved as they normally would be.)

Figure 1.—HIP. The physician's thumb is on the pubis and the middle finger is on the anterior superior iliac spine.

The leg is internally rotated if possible. Most often the inflamed hip joint will be held in external rotation, flexion and abduction since this position permits maximal distension of the capsule.

A point is selected two fingerbreadths below the center of a line drawn from the anterior superior iliac spine to the pubis, and about 2 to 3 cm lateral to the femoral pulse. The needle is inserted and when it strikes the bone it is withdrawn slightly.

Figure 2.—KNEE. The knee is flexed 90 degrees. The needle is inserted in the triangular area between the patella tendon, medial condyle and medial tibial plateau.

This is the most frequently injured or inflamed joint of the extremities. It contains the largest synovial pouch in the body. The anterior medial approach to this joint, aiming the needle between the posterior aspect of the patella and the anterior surface of the medial femoral condyle, is the one most frequently advocated. We prefer inserting the needle into a triangular area formed by the medial edge of the patella tendon, the anterior-inferior border of the medial condyle and the medial tibial plateau. The latter approach is easy and will prevent possible damage to the patella caused by probing while attempting to insert the needle into a minimally distended joint.

Figure 3.—ANKLE. The needle is inserted anterior and lateral to medial malleolus and medial to tendon of tibialis anticus.

This joint is approached 1 cm above and lateral to the tip of the medial malleolus. The needle is aimed at the joint just medial to the tendon of the tibialis anticus.

Figure 4.—SHOULDER. Needle is Inserted below coracoid process, just medial to the head of the humerus and angled 10 degrees toward midline.

Shoulder effusion always causes a bulge anteriorly. The point of insertion of the needle is just medial to the head of the humerus and below the tip of the coracoid process.

mediately after completion of the aspiration. If it is not practical for the patient to fast for at least ten hours before the joint is aspirated, the glucose determination is omitted, for only after fasting is the difference in glucose value between the synovial fluid and the blood significant. The degree of decrease in synovial fluid glucose content depends upon the glycolytic characteristics of the causitive organism.

The mucin clot test is performed by mixing

Figure 5.—ELBOW. Needle is inserted in center of triangle formed by lateral border of olecranon, lateral condyle and radial head.

The aspiration site is within a triangle formed by the lateral border of the olecranon, the posterior curvilinear margin of the lateral condyle and the posterior edge of the radial head.

Figure 6.—WRIST. Needle inserted distal to radius and to ulnar side of "anatomical snuffbox." Note extensor pollicus longus tendon lying to radial side of paracentesis site.

2 ml of synovial fluid collected in the fourth tube with 1 ml of 3 percent acetic acid. The character of the clot[3,4] is then interpreted in 30 minutes to an hour. A good clot is a thick, tight ropy curd with a clear supernatant (Figure 8A). A fair clot consists of a soft mass which occasionally is friable and the supernatant is slightly turbid. A poor clot is one in which a few shreds of material or a friable small clot with turbid supernatant is formed (Figure 8B). If there are only a few flecks of precipitate in a very cloudy supernatant (Figure 8C), the clot is very poor.

The quality and quantity of mucin undergo changes in response to synovial inflammation. These changes are manifest in a lowering of the viscosity of synovial fluid and in the character of the mucin clot.

Table 1 gives criteria for rapid classification of

Figure 7.—DIGIT JOINTS. Needle is inserted on dorsum of digit, at level of joint, to one side of extensor tendon and is angulated 15 degrees distally.

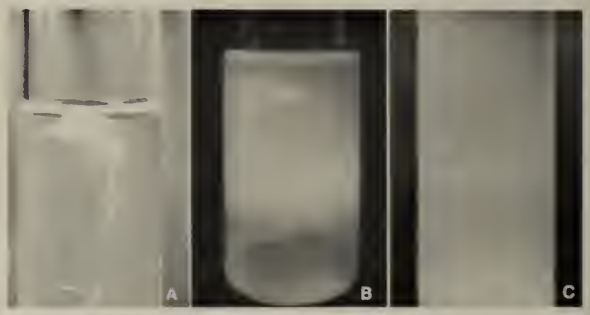

Figure 8.—QUALITATIVE MUCIN PRECIPITATION TEST. A—Normal Clot; B—Fair Clot; C—Poor.

the synovial fluid findings. Between Group I, which encompasses the changes associated with trauma, and Group III, which shows the characteristic findings in septic joints, there is an intermediate group (Group II) in which the synovial fluid findings related to the traumatic and the aseptic groups tend to overlap. For rheumatic fever and systemic lupus erythematosus the overlap is mainly between Group II and Group I, whereas for gouty arthritis and rheumatoid arthritis the overlap is in the other direction, from Group II to Group III. The highest viscosity is in normal fluid and it decreases progressively in Groups II and III. Normal fluid is clear amber; turbidity begins in Group I and becomes more pronounced in the remaining two groups.

Normal fluid does not clot spontaneously. Septic fluid clots readily. Fluid from a traumatized joint is in between, with a tendency to clot. Severe inflammatory reactions make the synovial membrane more permeable to albumin and globulin. The very large molecular protein fibrinogen, normally not present in synovial fluid, enters the synovial cavity and the fluid then has the capacity to form a spontaneous fibrin clot.

TABLE 1.—*Classification of Synovial Fluid Findings*

	SYNOVIAL FLUID						
	Appearance	*Relative Viscosity*	*Spontaneous Clot*	*Mucin Clot*	*Leukocytes mm³*	*Percent Polymorphonuclear*	*Sugar Difference mg/100 ml*
	NORMAL						
	Clear	*Very Viscous*	*0*	*Good*	*10 to 180*	*0-25*	*<10*
GROUP I: TRAUMATIC							
Traumatic arthropathy Degenerative joint disease Neurogenic arthropathy Pigmented Villonodular synovitis Osteochondromatosis, osteochondritis dissecans	Clear to slightly turbid	Mildy reduced	0 to 2 plus	Good to Fair	300 to 3,000	0-30	<20
GROUP II: INTERMEDIATE							
Those which tend to overlap with Group I: Rheumatic fever Systemic lupus erythematosus Hypertrophic pulmonary osteoarthropathy	Slightly turbid to turbid	Moderately reduced	1 plus to 3 plus	Fair to Poor	3,000 to 20,000	40-80	10-40
Those which tend to overlap with Group III: Gouty arthritis Rheumatoid arthritis Reiter's disease							
GROUP III: SEPTIC							
Infectious arthritis Tuberculous arthritis Gonococcal arthritis	Turbid to very turbid	Greatly reduced	4 plus	Poor to very Poor	15,000 to more than 200,000	50-100	>40

The mucin clot is good in normal fluid, and usually is fair to poor in the intermediate group. A very poor clot is noted in Group III. The cell count is usually 10 to 108 per cu mm in the normal group and reaches 200,000 or more in the septic group. Any cell count over 3,000 usually indicates conditions which fall into the intermediate group. Cell counts of more than 15,000 are usually found in septic conditions. The percent of polymorphonuclear cells increases from Group I to III. The difference between the glucose content of the synovial fluid and of the blood is less than 10 mg per 100 ml in normal synovial fluid. It increases slightly in traumatic conditions and reaches as much as 40 or more with sepsis.

Fractures of joint surfaces, trauma to fat pads and synovium, and degeneration in far advanced rheumatoid arthritis can produce free fat globules in synovial fluid.

Xanthochromic fluid and bloody fluid is frequently found in a bloody tap, traumatic arthrosis, pigmented villonodular synovitis and hemophilic arthrosis. Joint fluid from a bloody tap or traumatic arthrosis will separate into a precipitate and supernatant. The supernatant will be clear after standing for an hour or more. However, the supernatant will be found to be xanthochromic in pigmented villondular synovitis and hemophilic arthrosis.

Sodium biurate crystals can be found in the aspirate from gouty joints. These crystals are birefringent and easily identified under a polarizing microscope on a fresh wet specimen. Calcium phosphate crystals in cases of "pseudogout" must be differentiated from sodium biurate crystals. Uricase readily digests the latter but not the former.

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The Use of Propoxyphene Napsylate in the Treatment of Heroin and Methadone Addiction

DARYL S. INABA, Pharm D, GEORGE R. GAY, MD, CRAIG A. WHITEHEAD, MD, and JOHN A. NEWMEYER, PH D, *San Francisco,* and DAN BERGIN, BA, *Sacramento*

The use of methadone in the treatment of heroin addiction continues to be controversial. Propoxyphene napsylate (Darvon N®) is a possible alternative and a pilot study was conducted to test its acceptability, safety and clinical efficacy in treating long term, "multi-relapse" heroin addicts.

Findings indicate that propoxyphene napsylate suppresses many of the symptoms associated with opioid withdrawal phenomena. It should be viewed as a very promising therapeutic tool to be used in conjunction with psychological counseling and socio-vocational rehabilitation in detoxification and maintenance therapy for heroin or methadone addiction.

STIMULATED BY THE continuing controversy about the use of methadone in the treatment of heroin dependence, there has been much interest recently in finding a substance with the beneficial effects of methadone but without its undesirable characteristics. Initial research by Tennant[1,2] has suggested that propoxyphene napsylate (Darvon N®) may be an effective and safe substitute for methadone in both maintenance and detoxification therapy.

Pioneering methadone research by Nyswander and Dole[3-6] encouraged the establishment of a multitude of methadone treatment programs throughout the United States. Unfortunately, methadone has proved to be yet another physically addicting opioid drug which, moreover, is associated with pronounced withdrawal phenomena. Also, the much longer biological half-life of methadone, compared with that of other opiates, is seen to produce prolonged and complicated overdoses.[7-11] These problems, plus reports of lessened libido and male impotence,[1] have reduced the acceptance of methadone by the heroin addict population.

Tennant[1] has noted that in the Black population of the Watts area in Los Angeles, one response to this controversy has been an almost "evangelical acceptance" of propoxyphene napsylate (PN) therapy. Moreover, in a nine-month study, he found that PN had specific advantages over methadone for use in the treatment of heroin addiction. Of a total of 372 persons addicted to heroin, 230 were reported to be satisfactorily detoxified as inpatients, 50 were detoxified as outpatients and 92 were maintained (for a period of greater than 21 days) on PN as outpatients. Initial daily dosages of PN ranged from 300 mg to 1,600 mg, and although most were well above the recommended maximum daily dose of 8 mg per kg of body weight,[12] no toxicity was noted. He noted that therapy with PN not only had all the benefits of methadone therapy but, further, produced minimal

From the Haight-Ashbury Free Medical Clinics' Drug Detoxification, Rehabilitation, and Aftercare Project, San Francisco, and the Heroin Detoxification Ward, Aquarian Effort, Sacramento.

Submitted January 8, 1974.

Reprint requests to: G. R. Gay, MD, Director of Clinical Activities, Haight-Ashbury Free Medical Clinics, 529 Clayton Street, San Francisco, CA 94117.

physical addiction, resulted in no reports of impotence, induced an "unpleasant euphoria" (thus lending to negligible incidence of voluntary abuse), could not be injected, produced unpleasant effects when ingested simultaneously with other commonly abused drugs and had a low overdose potential. Of special interest were fairly consistent (71 percent) reports of a diminished or absent "yen" (craving for heroin) with PN therapy. The theme of "something works with PN" was repeatedly expressed by the population of this study.

Tennant's success has been paralleled by Bergin* in Sacramento. This research consisted of a well controlled, five-day inpatient PN detoxification program. Bergin's four-month, 178-patient study used much smaller doses of PN (an average daily high dose of 747 mg) than were used in Tennant's study. PN was administered in multiple daily dosages (100 to 200 mg four to six times per day) based upon observed withdrawal symptoms. No distinguishable side effects from PN were noted in any of the 178 patients. Bergin concluded that PN produced no physical dependence over this short period of administration and could be considered a safe drug when dispensed in the manner described. In addition, this study population (73 percent White, 14 percent Black and 10 percent Chicano, ranging from age from 18 to 48 years) was found to have a favorable attitude toward the use of PN for detoxification. Furthermore, the patient treated with PN was found to be more receptive to direct individual and group counseling. Emphasizing that a "varied support" of the client should be continued as the major part of therapy, Bergin nevertheless recognized PN to be a key drug in his methods of treating heroin addiction.

Recent investigation by List,* in Baltimore, has documented the effectiveness of PN in the detoxification of methadone patients. In using methadone for heroin detoxification in recommended decremental dosage alone, List observed severe opioid-like withdrawal symptoms. Patients had difficulty keeping jobs and there were abrupt social and personality changes when methadone dosage was decreased to 30 to 50 mg per day. Because of this observed phenomenon, a study of 80 patients (89 percent male, with 50 percent Black and 50 percent White) was arbitrarily divided into two treatment groups. One group was detoxified by decreasing methadone from established maintenance levels in decrements of 5 mg per week, and the second group was given 200 mg of PN in addition to 45 mg of methadone. Amounts of PN were then increased or maintained during detoxification as methadone dosage was decreased by 5 mg per week. After successful methadone detoxification, PN was then gradually reduced. Findings indicated that 33 percent of the patients receiving PN were successfully detoxified, compared with only 6 percent of the group treated with methadone alone. It was also noted that the propoxyphene group was detoxified from methadone approximately twice as rapidly. In addition, they were better able to hold jobs and they reported fewer physical complaints during detoxification.

Cases of propoxyphene hydrochloride (PCl) abuse and true physical addition,[13-20] along with many cases of PCl overdose and death,[21-26] have been reported in the medical literature in recent years. The potentially lethal consequences of propoxyphene overdose, with intoxification frequently complicated by pulmonary edema, convulsions† and generalized central nervous system depression,[22] warrants further elucidation here as regards the water solubility of its two common clinical salts. Propoxyphene napsylate is only slightly soluble in water (1.5 mg per ml), whereas PCl is highly soluble in water (2 gms per ml).[27] It follows, then, that because of this crucial distinction in water solubility, PN may well have a lower overdose potential than PCl. Indeed, a 9 gram dosage of PN has been survived without sequelae.[1,2]

Methods

A pilot study, suggested by the research of Tennant,[1,15] Bergin and List (unpublished data), was begun in August, 1973, to study outpatient detoxification of heroin addicts with the use of PN. Volunteer patients from the Drug Detoxification, Rehabilitation, and Aftercare Project of the Haight-Ashbury Free Medical Clinics were selected for the study.

The clinic has used PCl in prescribed therapeutic analgesic dosages since it became clinically available, as a part of its symptomatic therapy for opiate withdrawal;[28] but it had never before employed PN either in large (600 to 1,400 mg per day) dosages or as the sole drug in the management of heroin withdrawal symptoms.

Thirty-two patients were selected. The basis for admission to the PN program was a demonstrated,

*Unpublished data, see Addendum to References

†Convulsions appear to be particularly common with propoxyphene overdose, much less frequent with other opiate and opioid drugs.

continued refractiveness to other available treatment approaches and documented frequent recidivism into heroin or multiple-drug abuse.

Each patient selected was interviewed informally in a non-punitive fashion, and was encouraged to freely state any opinions or observed subjective effects of PN therapy.

PN was administered to each client twice a day. The first of these daily doses could therefore be administered to the patient while he was under the direct observation of the clinic staff. In this manner, the responses to PN doses were observed and evaluated daily for a few hours post ingestion. A second dose of PN was determined from these evaluations. The second dose was then given to each patient to be taken at home.

The only other drugs administered to these patients during the study period were either chloral hydrate or flurazepam (Dalmane®). These were dispensed for sleep during the initial three to four days of acute opioid detoxification.

Results

Of the 32 subjects chosen for this program, 22 (69 percent) were male and ten (31 percent) female. The age range was typical of that of all clinic patients, with 6 percent less than 21, 38 percent between 21 and 25, 34 percent between 25 and 30, and 22 percent over 30 years old. Twenty-eight (88 percent) were Caucasian, three were Black and one was Asian. Inquiry into the length of time since first addiction disclosed that two (6 percent) had been addicted for more than ten years, nine (29 percent) had been first addicted between five and ten years ago, eleven (35 percent) between three and five years ago, five (16 percent) between two and three years ago, and four persons (13 percent) had first developed a heroin habit less than two years ago. Six of the patients (20 percent) reported "light" habits ($20 per day or less), while ten (33 percent) described "heavy" habits ($50 per day or more); the remainder were in the "moderate" habit range ($20 per day to $50 per day).

Many of the patients in the PN program had been seen for some length of time at the clinic. Fully one-third of the total sample had been to the clinic more than 50 times by the beginning of November, 1973. This is important because the PN sample may be biased in favor of long-term addicts who have had many relapses and therefore may represent something of a hard core.

The duration of therapy with PN extended from one to sixty-six days, with the majority of patients, 19 (69 percent) being seen for periods of five to thirty days. PN dosages for acute opiate withdrawal symptoms ranged from 600 mg to 1,400 mg per day.

TABLE 1.—*Results of Urinalysis in PN Program*

	Specimens	*Percent*
Total urine specimens received	182	
Patients refusing to give urine specimen	12	7
Total negative results for drugs	6	3
Positive results for drugs:		
Propoxyphene	137	75
Phenobarbital	43	24
Any illicit drug	53	29
Morphine	34	19
Codeine	13	7
Methadone	6	3
Amphetamine	5	3
Barbiturate	2	1
Cocaine	0	

Two methods of evaluating the success of the PN program were used: urinalysis and counselor evaluation. Results of urinalysis are shown in Table 1.

The patients seemed to be taking the PN much as scheduled and were not submitting someone else's urine. The urine was significantly freer from drugs than that of patients not in the PN program (29 percent of urine specimens tested positive for drugs as opposed to 39 percent for clinic patients generally during 1973). Abuse of amphetamines and barbiturates appeared especially low.

Subjective Data from Patients in PN Program

Reports of Heroin Blockage

Seventeen patients acknowledged concurrent use of heroin after taking PN. Seven of these (41 percent) reported no interference or block of heroin effects. Seven (41 percent) reported a partial block and one reported a total blockage of effects. Two patients reported a slight potentiation of heroin effects.

Reports of Decreased Libido During PN Therapy

Three patients reported a decreased libido not noticed before beginning PN therapy. Two patients reported a decreased libido, but admitted to noticing it before starting PN therapy (probably resulting from heroin and opiate abuse). One patient experienced an increase in libido when doses of PN were decreased. The remaining patients made no comment in this regard.

TABLE 2.—*Frequency of Side Effects Reported by Patients Taking PN*

Feeling of detachment, a psychotogenic drug-like reaction	4
Dizziness	1
Drowsiness	2
Nervous and "Jittery" after PN ingestion	2
"Shaky" before each morning dose of PN	2
Headaches	2
Morning "Hangover"	1
Blurred vision	1
"Metallic" or "Funny Darvon-N" taste	2
"Darvon-N Smell" to everything	1
"Tingling" numbness of teeth, gums, or mouth	2
Leg and joint cramps	1
Upset stomach	2
Constipation	2
Emesis	1

Opioid Withdrawal Symptoms Suppressed by PN

Ten patients (31 percent) reported no withdrawal symptoms while taking PN, as opposed to only three (9 percent) who reported that it did not help. Nineteen patients (59 percent) reported almost total suppression of symptoms. Fifteen (47 percent) reported insomnia which persisted for the first three days but improved on or about the fifth day (Tennant's[1,15] and Bergin's [unpublished] data support this). Consistently, the usual requests for additional medications (sedatives, tranquilizers and anticholinergics) diminished significantly between the third and fifth days. The patients often stated that they felt much better at that time and that Darvon N was working. Ninety-one percent claimed a decreased heroin "yen" while taking PN.

Report of Side Effects

Twelve patients (38 percent) reported no side effects and eleven (34 percent) reported some side effects. In only two cases were side effects (emesis and blurred vision) severe enough to cause the termination of therapy. The side effects and frequency of reports are shown in Table 2.

Report of Propoxyphene Withdrawal Symptoms Precipitated by Tapering or by Termination of PN

Six patients (19 percent) reported no withdrawal symptoms upon termination of dosage. Twenty patients offered no comments or were unavailable to follow-up. Six patients (19 percent) reported withdrawal symptoms (Table 3).

Interaction with Other Abused Drugs

Codeine was the most frequent concurrently abused drug; this was confirmed by urinalysis (7 percent of all urine specimens collected). Also noted were methadone (3 percent), amphetamines (3 percent) and pentobarbital (1 percent). Some patients alleged concurrent abuse of methaqualone (2 percent) as well. The program intermittently dispensed phenobarbital, chloral hydrate, flurazepam and diazepam for sleep. No interaction with any of these drugs was reported. Three patients alleged a potentiation effect of alcohol when taken in combination with PN.

TABLE 3.—*Withdrawal Symptoms Reported in PN Program*

Symptoms	*Days of Therapy*
Severe heroin-like withdrawal symptoms from abrupt termination of PN	33
Mild heroin-like withdrawal symptoms on abrupt termination of PN	30
Same as above	40
Increased anxiety noted from a quick 5-day tapering of PN	39
Increased anxiety and nervousness from abrupt termination of PN	10
Chills, shakes, aches and pains of low intensity from abrupt termination of PN	16

Propoxyphene Mood Changes

Nine (28 percent) patients noted pleasant euphoria after taking PN and one noted dysphoria. In addition, nine patients reported a "drugged" feeling within one hour after oral ingestion of PN (usually with the higher dosages dispensed). Pinpoint pupils, some slurring of speech and a definite "drugged state" were observed in some cases. Sleep patterns were noted to improve and "even out" after the third to fifth days.

Diversion

One case of diversion of PN to outside "street" use noted. (Tennant reports this is a common practice in his population.)

Hepatitis

Two cases of hepatitis, as determined by liver profile, were observed in the study population. Clinically, these were probably not related to PN therapy.

Discussion

Though compromised by the lack of absolute control in an outpatient population, this pilot study nonetheless clearly delineates a number of important clinical considerations. PN is felt to possess some of the disadvantages of methadone,

and yet appears to have some significant advantages. From the data accumulated, it is felt that PN may be viewed as a promising therapeutic adjunct to opiates in the management of physical dependence. However, a long term program of detoxification probably would be best suited to the hard-core, multi-relapse population studied. It is felt that this longer treatment period would enable the patient to develop a fuller counselor relationship and would provide adequate time for voluntary entrance into socio-vocational rehabilitation programs before termination of medication. As ever, total abstinence from drugs by any drug-abusing individual is a multi-disciplinary problem, and one not to be easily dismissed as remedial by purely pharmacotherapeutic methods. The patients in this study who responded best to PN therapy were repeatedly noted to have established a much "tighter" counselor relationship than those who responded poorly.

A clinically observed improvement in the subjective effects of PN (including alterations in mood) during the third to fifth days of therapy was noted in our study population and was also observed by Tennant[1,15] and Bergin (unpublished data). This may prove to be a very significant observation in view of the current hypothesis that the inhibition of the heroin abstinence syndrome of PN is, in fact, due to its unconjugated metabolites, nor-propoxyphene and bi-nor-propoxyphene. Studies by McMahon, et al[29] have shown the presence of one major propoxyphene metabolite in humans: nor-propoxyphene. It was also observed that the concentration of nor-propoxyphene in human plasma was much higher than that of propoxyphene itself and that it had a substantially longer biological half-life. McMahon further suggests that nor- and bi-nor-propoxyphene attain measurable plasma concentrations 75 hours after oral administration of propoxyphene. Thus, a possible correlation between clinical data and the proposed active metabolite hypothesis is reported.

Significant findings of this pilot project included:

- An almost universal acceptance that "PN works" by the group studied.
- PN suppresses the symptoms of opiate withdrawal and, in sufficient dosage, significantly diminishes the "yen" of heroin craving.
- PN is effective in a single or in a divided (twice a day) oral dose.
- A stabilization of mood and affect appears after three to seven days, along with improved sleep patterns.
- Although PN is capable of producing habituation and physical dependence, the withdrawal phenomena of PN are less than those produced by either heroin or methadone.
- Acute or chronic toxicity does not appear to be a significant factor in the dosage employed.

Our results suggest three areas for clinical study using PN in the management of heroin or methadone dependence:

1. *Heroin Detoxification*

(a) Five-day therapy with multiple low daily PN dosages.

(b) Twenty-one-day inpatient or outpatient therapy with PN administered once or twice daily.

(c) Long-term outpatient detoxification of one to six months duration with PN given once or twice daily.

2. *PN Maintenance*

3. *Methadone Detoxification*

(a) Graduated supplementation with PN correlated with decreasing methadone dosage, followed by a graduated decrement of PN.

(b) Abrupt substitution of PN for methadone, followed by graduated decrement of PN.

The current limiting factors of PN therapy have to do with acute and chronic toxicity. Mindful of the severe consequences of acute propoxyphene toxicity, a divided dosage regime is suggested, allowing for some drug-symptom observation in addition to a greater safety margin.

Kiplinger et al[30] have reported ten cases of anicteric hepatitis (probably not related to drug use) in a study population of prison inmates administered PN and PCl salts chronically for six months. Also, liver enlargement, fatty liver changes and increased serum liver enzymes have been previously noted in rats and dogs treated for short terms with high doses of hydrochloride and napsylate propoxyphene salts.[31]

Further research and full assessment of the biopharmaceutical and pharmacokinetic properties involved with absorption of PN from the human gastrointestinal tract must be undertaken. Future double-blind human studies and controlled protocol are obviously needed to establish safe standards, especially in regard to PN dosage. Clearly, PN shows great promise in detoxification or mainte-

nance substitution therapy for opiate and opioid dependence. What is needed now is a clinical and laboratory examination that is deliberate, thorough and highly disciplined.

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Addendum:

Unpublished data reported in this study were drawn from the following:

1. Bergin D: Caseload statistic summary of Darvon-N detoxification. Unpublished data from The Aquarian Effort, 2104 Capitol Avenue, Sacramento, California, Nov 13, 1973;

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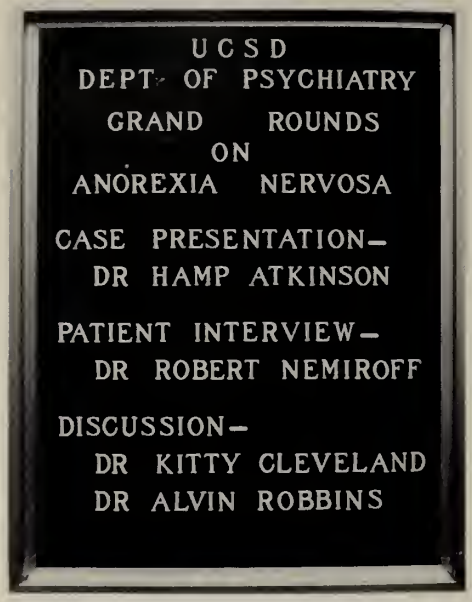

Anorexia Nervosa

Based on Psychiatric Grand Rounds held at the San Diego Veterans Administration Hospital, a teaching facility of the School of Medicine, University of California, San Diego, in October 1973; edited by Barbara Blomgren, BA, and Leighton Huey, MD.

Dr. Atkinson:* The patient is a 41-year-old divorced, unemployed clerk who entered the hospital complaining, "I was unable to take care of myself." She was born in Chicago, lived in Sweden from the age of one to the age of six, and then returned to California to live permanently. The patient has a long history of depression and associated weight loss, beginning at the age of 15 when, during several months of absence from her father, her weight dropped from 115 to 90 pounds. At the time she rejoined her father her weight increased rapidly, to a maximum of 135 pounds at the age of 18. During that first period of weight loss she became amenorrheic. Menstruation resumed between the ages of 17 and 21, at which time she again became ameorrheic, and she has remained so. In adolescence she had few if any dates, secondary to her mother's insistent sexual prohibitions. When she was 19 years old, she left home to join the Air Force, and a year later she married an Air Force officer. After three months the marriage was annulled at her mother's insistence, and from the age of 20 the patient lived in the parental home. She found employment and did well as a clerk and stenographer.

At the age of 20 she began using 10 to 12 dextroamphetamine sulfate (Dexedrine®) tablets daily for fatigue and depression and continued this for 14 years. She said she had not used amphetamine since 1966. For the last 20 years her weight had varied between 75 and 90 pounds, with one all-time low of 58 pounds when she was 34 years old. Around the age of 24 she had a three-month episode of depression and a weight loss of 20 pounds. She was admitted to hospital and after an upper gastrointestinal series and barium enema she was told that her weight loss was due to emotional problems. There was no psychiatric follow-up. She then did reasonably well until, seven years before the present admission, she suffered severe depression, rectal prolapse secondary to laxative abuse, lost weight to 58 pounds, and was admitted to hospital to gain weight. At the end of two months in the hospital she had regained almost all of her lost weight, but after discharge she began to have vomiting after every meal, which continued to the present admission.

About four years ago her father died of carcinoma of the stomach, and she gave up her job to devote full time to the care of her invalid mother. In 1971, the patient had resection of a malignant melanoma. Two years before admission she became increasingly depressed because

*J. Hamp Atkinson, MD, Resident in Psychiatry.
Reprint requests to: Barbara Blomgren, Editor, Department of Psychiatry, UCSD School of Medicine, La Jolla, CA 92037.

of her mother's illness, and she attempted suicide by chloral hydrate overdose in her mother's presence. She was admitted to hospital and there was diagnosed as having passive-aggressive personality disorder. She was treated with imipramine hydrochloride (Tofranil®), 75 mg per day. Her mother died of multiple cardiovascular accidents shortly after the patient's suicide attempt. A few months later the patient re-entered the hospital with complaints of depression. She was diagnosed as an emotionally unstable personality, treated with thioridazine (Mellaril®), 100 mg per day, and discharged to outpatient follow-up at a community mental health center. During the next year she was followed with monthly group therapy and treated with diazepam (Valium®) and amitriptyline hydrochloride (Elavil®) in psychotherapeutic amounts.

Her appetite remained satisfactory until about nine months before admission when she became increasingly depressed and anorectic, possibly secondary to problems with her boy friend and her female roommate. Four months ago, she entered our outpatient clinic because of depression and weight loss. She was seen in individual psychotherapy and treated with doxepin hydrochloride (Sinequan®), 150 mg per day. Despite treatment she lost 20 pounds during the next four months. One month ago, results of a complete endocrinological workup (including growth hormone, follicle-stimulating hormone, leutinizing hormone, and cortisol) were within normal limits, as were results of skull and upper gastrointestinal x-ray studies. Two weeks before admission she experienced indistinct auditory hallucinations; she said her mother cried over and over again to her, "Eat, eat!" She began interpreting noises from the air conditioning as voices from a crowd of people. Her outpatient therapist recommended admission to hospital because of the persistent weight loss and severe depression.

Her family history is significant in that she describes her childhood as relatively happy, but says her father was an alcoholic who was passive and distant and her mother was dominant and controlling. A maternal aunt suffered from affective disorder and killed herself.

On admission to hospital, the patient, who was 5 feet 3 inches tall and weighed 66 pounds, was thought to have a unipolar depression and possible anorexia nervosa. We began giving her Elavil, 200 mg per day, and undertook a behavior modification program linking progressive inpatient privileges to weight gain. The depression cleared rapidly, and she gained 13 pounds during the first five weeks in hospital. On the ward she was hostile, dependent and manipulative, voicing numerous somatic complaints. One episode of self-induced vomiting was witnessed by the staff and denied by the patient. We presume that she induced the other episodes of vomiting in the hospital, as she probably did the ones she describes having had after every meal for seven years.

She is being seen by two therapists simultaneously; administrative and therapeutic functions are assigned to different persons because of her continuous manipulative behavior. She really was unable to care for herself, unable to express her feelings and unable to see herself as an effectual person. Accordingly, during therapy we are making every effort to include her as an active member of the team in planning her treatment, and to get her to recognize her emotions, to express them, and to feel more significant as a human being. I think we have been moderately successful.

Dr. Lowell Storms:* The patient was given psychological tests two days after admission to hospital. A Minnesota Multiphasic Personality Inventory (MMPI) showed severe depression, marked anxiety, ruminations, low self-confidence, and a tendency to shyness and social withdrawal. There was also evidence of considerable character disorder, with passive-aggressive and passive-dependent features. She tends to be self defeating and have poor persistence and motivation. She has difficulty delaying the relief of anxiety and tends to rationalize her hostility and externalize it. She seeks dependent and immature relationships with men toward whom she might play a daughter role. There is evidence of vulnerability to problems with drugs or alcohol. The evidence suggests that she could become disorganized under stress and might be a borderline schizophrenic.

(The patient, whom we shall call Louise Jackson, was escorted into the room and introduced to Dr. Nemiroff, who interviewed her before approximately 100 staff members and residents.)

Dr. Nemiroff:† Hi, Louise. Would you have a seat here? Let me see if I can help you with the microphone — please excuse our technology. Thank you very much for coming here today,

*Lowell Storms, PhD, Professor of Psychiatry.

†Robert Nemiroff, MD, Assistant Clinical Professor of Psychiatry.

Louise. How do you feel about meeting here in front of this large group?

Patient: I don't really know, but I see some faces I recognize.

DR. NEMIROFF: You do?

Patient: Um hum.

DR. NEMIROFF: So you don't feel so all alone?

Patient: No.

DR. NEMIROFF: You're not. We're here with you. Louise, we've heard from Dr. Atkinson a little bit about some of the problems you've been having in the past and currently. But we were hoping to hear from you, in your own words, your understanding of the difficulties you have and what brought you to the hospital. Could you tell us?

Patient: Oh, I don't really know. Could you just ask me questions? I could say yes or no. To start with anyway.

DR. NEMIROFF: What didn't you know about my question?

Patient: Well, it was clear, but I didn't know where to start. It's kind of a long, drawn-out thing.

DR. NEMIROFF: I see.

Patient: It's something that's happened to me before.

DR. NEMIROFF: Uh huh.

Patient: But this time it really got bad, and I became very frightened.

DR. NEMIROFF: This time it became particularly bad, and you got frightened.

Patient: Yeah.

DR. NEMIROFF: Maybe that's a place to start. If you can tell us a little bit about exactly what happened right before you came to the hospital, and how it was bad for you and how you got frightened, that would be a way in which we could get into this a little bit.

Patient: Well, I have a roommate that's had very high blood pressure, and she wasn't feeling too well. She was in bed most of the time. And then I practically lost so much weight I didn't have any strength left, so I was in bed most of the time too. And between the two of us we didn't do any cooking to speak of, and I wasn't too hungry anyway, and I was having trouble retaining my food. I know Kathy Porter [the outpatient therapist] knows a little bit about it because I was coming here as an outpatient to see her. And she arranged it so I would be admitted here to the hospital.

DR. NEMIROFF: Well that's good. I'm glad that you came.

Patient: I am too. I was ready to leave, you know, the first week.

DR. NEMIROFF: You were?

Patient: I'm glad I stayed though. It's been very beneficial.

DR. NEMIROFF: Uh huh. What was it that was troubling you that first week? Why did you want to leave?

Patient: I thought there were too many restrictions, and I got kind of scared. I didn't know what I was getting into.

DR. NEMIROFF: Too many restrictions. People weren't letting you do what you wanted to do?

Patient: No. But I've acquired quite a few privileges now. I weighed 79 yesterday, and I weighed 80 this morning.

DR. NEMIROFF: Uh huh.

Patient: So I think that's going in the right direction.

DR. NEMIROFF: How do you see yourself at this point? On the thin side?

Patient: Yeah, I think so.

DR. NEMIROFF: How much weight do you think you need?

Patient: Well, I want to gain at least 10 more pounds before I leave the hospital. But there are other things that go along with that. I have to change my feelings about a lot of things—the reactions that I have—the way I meet people, and how I talk. Because I am kind of a shy person to begin with. Don't sound that way right now, though, do I?

DR. NEMIROFF: No, you're doing very nicely, and starting to express things a little bit, and I'm starting to get a better idea of things. I'd like to go back for a moment to the kind of thing that brought you into the hospital. You say you were there with your roommate, and there were the two of you there in the room, and she got sick.

Patient: Yeah, well she had high blood pressure, and she was in the process of getting the medicine changed, and it affected her so that she got dizzy every time she got up, and I was afraid she'd fall down or something, you know.

DR. NEMIROFF: I see. Sure.
Patient: So I was kind of worried about her.

DR. NEMIROFF: You were kind of taking care of her.
Patient: Well, we were taking care of each other, more or less. We didn't do a very good job of it, I'm afraid.

DR. NEMIROFF: I see. Uh huh. Did she do some of the cooking? Who did the cooking between the two of you?
Patient: Well, we ate more like cottage cheese and sandwiches. We both went to a restaurant, or like that. But I was living on instant breakfast that last week I was home. That was the only thing I could keep in my stomach. And I was afraid there might be something organically wrong, but there wasn't.

DR. NEMIROFF: Uh huh. What did you think might be organically wrong with you?
Patient: Well I had had a GI series, and the doctor did tell me that my stomach emptied a lot slower than other peoples', and I knew that I had to keep something in my stomach all the time, and the only thing that I could retain was that instant breakfast.

DR. NEMIROFF: What were some of your feelings when your roommate got sick?
Patient: Well, I was frightened for her, and one of the reasons we decided to move in together to begin with was the fact that she didn't want to live alone in her trailer, and I didn't want to live by myself, and I had no real home, so she just threw in her lot with me, financially.

DR. NEMIROFF: And then she couldn't keep up her end because she got sick and she took to bed and then you became upset with that. I see. That was a difficult situation because here you were depending on her and hoping that she would be a help, and yet she was depending on you.
Patient: Well, I realize now that the only person I can depend on is myself. I'm beginning to find that out more and more. And I know that when I get back home she'll be coming back with me, and she's been getting a lot better too since she's been gone, and she's been forcing herself to do more things, and I've been pretty busy here. There's a lot of things that I've had to do.

DR. NEMIROFF: How has your physical health been in general?
Patient: It's been good.

DR. NEMIROFF: Do you have any problems, or anything that concerns you?
Patient: No. No, I haven't had anything wrong with me.

DR. NEMIROFF: In the past?
Patient: Oh, in the past I've been hospitalized several times.

DR. NEMIROFF: For what?
Patient: Well, I had skin cancer once. And several times I've lost weight. And then I had rectal surgery in 1966. And I stayed quite a while in a hospital to gain weight before they did the operation on me. And then I went back there for another month and a half to recuperate.

DR. NEMIROFF: How are you doing with the skin cancer?
Patient: Oh, it was all taken out.

DR. NEMIROFF: It was all taken care of? That's not on your mind or troubling you?
Patient: No. I just have a big long scar down my back. No, I'm not worried about that at all. Since I've been here, you know, I haven't had any trouble with food or anything.

DR. NEMIROFF: Good.
Patient: So I'm working along pretty well.

DR. NEMIROFF: You like our cooking here?
Patient: Yeah. Yesterday I had four milkshakes.

DR. NEMIROFF: You know, Louise, we're talking about your current situation a little bit. I wonder if you and I could take a bit of a trip into the past? Is that all right?
Patient: How far back do you want to go?

DR. NEMIROFF: Let's go all the way back. Well, let's see. Let's at least go as far back as when you were 15 or so and you first started to have these difficulties. Could you tell me a little bit about that?
Patient: Well, my mother and I took a trip to Sweden, and we went over in the month of March, and the water was pretty rough, and the ship almost went down.

DR. NEMIROFF: Really?
Patient: Yes, three times—one side to the other—and the furniture and everything just got pulled loose from the floor.

DR. NEMIROFF: My gosh!
Patient: Yes, it was a real mess, and when I got

over to Sweden I got influenza real bad, and it was real cold over there and snowing, and I was homesick. I had just started high school, and my mother took me out of school to go over there, and the idea was that were were going to live over there, and that was worse yet. And we left my dad over here.

DR. NEMIROFF: I see.

Patient: And when we got over there my grandfather said, no, he didn't want us to stay there because he said I wasn't going to be happy there, and he didn't like the politics there, and it wasn't going to be very beneficial for us, and so mother and I had to come back. But I was really sick over there, and I started losing weight, and I also stopped my menstrual periods, and when we came back I was under a doctor's care for quite a while, and I think I was all right until about the time I joined the Air Force, and then I gained up to about 135 pounds. And then after I'd been working for about four or five years, I was down at X Hospital, and they couldn't find anything wrong with me. I had lost weight then. Oh, and then I've been in Y Hospital on the psychiatric ward a couple of times. A very unpleasant experience.

DR. NEMIROFF: What did you gather from those experiences?

Patient: I didn't get anything from them. Just that I didn't want to go back there again. Every time I lost weight I ended up back in the psychiatric ward. And yet the doctors there couldn't do anything for me.

DR. NEMIROFF: You didn't get any idea of the kinds of things that were troubling you, what it was that led you to come to the hospital?

Patient: No. When I was getting the psychiatric care, my mother and father were both alive, and they blamed all my problems onto my mother. And then when my mother died I got the blame for all the problems when it was, you know, extremely difficult. But I was never aware of that because my mother always took care of me and it wasn't that I wanted to lean on her so much but she wanted me home.

DR. NEMIROFF: She wanted you home. Could you tell me about that? Why was it she wanted you home?

Patient: Well, she thought I'd live better at home, and she thought I'd have more money to spend if I lived at home. And it turned out that I bought a new car every couple of years and had a nice wardrobe. I enjoyed having somebody taking care of me to that extent. She did all the cooking and everything, but it was what she wanted to do herself. She said, "The only pleasure I have is your own happiness." And that's always stayed with me. And when she became ill and I took care of her, well I was in a different kind of role, and I did the best for her that I could at that time. She was in a wheelchair for over a year, and she did die finally shortly after she was operated on. She had a fractured hip. They went ahead and operated a little too soon. I didn't think she was strong enough. And she died, and I was left alone, and that was really a loss. I was scared.

DR. NEMIROFF: I can imagine. What were you scared of?

Patient: I didn't know what was going to happen to me. My father had died two years before that time, and I had lost my mother. I had relatives that lived nearby, and they kind of took over for me—helped me out.

DR. NEMIROFF: You were very alone. What were you afraid was going to happen on your own?

Patient: Well, I don't know. I was kind of sheltered about so many things, you know. So, I don't know. I was kind of leery of a lot of things.

DR. NEMIROFF: In the way that she took over, you were kind of fed by her continually.

Patient: Yeah, only I didn't realize the damage that I was doing to myself. I've found that out now.

DR. NEMIROFF: You mean there were pros and cons? You had the security of being with her and being in that relationship and there were nice things about it, but you were kind of robbed and cheated of your own development?

Patient: Yeah. But, you see, nobody ever brought those things to the front before, so I didn't, you know, wasn't aware of them. But I'm aware of them now.

DR. NEMIROFF: Yeah, it seems to me you are working on it.

Patient: Yeah, at times.

DR. NEMIROFF: Um hum, you really are. You're working with Dr. Atkinson and the ward psychotherapy program. How do you feel about the therapy and what is happening?

Patient: Well, it's been good for me, and I know

that the doctors and nurses spend a lot more time with their patients and they get to know them, you know, in and out. And they can help a lot more that way.

DR. NEMIROFF: I think you are getting a lot of help. I want to go back, this is a little bit personal, but I want to go back to talking about your mother. She died . . . and you went to the funeral?

Patient: No, we had no funeral for her. My aunt made up her mind that we didn't need a funeral for her; she was going to be cremated.

DR. NEMIROFF: No service?

Patient: I had a memorial service for her afterwards.

DR. NEMIROFF: You arranged your own service for her?

Patient: Well, the minister out there said he would be glad to do it.

DR. NEMIROFF: Did you cry during that time?

Patient: No, I didn't cry then, but I sure have cried a lot since. I was just too thunderstruck at first, you know.

DR. NEMIROFF: Sure. Was it at the service that you felt too thunderstruck by being left alone, and you couldn't cry?

Patient: Yeah, I think so. I cried the day that she died, and then I really didn't shed too many tears, but I've shed plenty since.

DR. NEMIROFF: Do you think about her frequently?

Patient: Not as much as I used to.

DR. NEMIROFF: What would you think about when you would think about her a lot?

Patient: I always visualized her the way she was before she died. She was in this hospital bed, and she had her leg in traction; she couldn't talk, and her hair was, you know, wrapped around her head, and she just didn't open her eyes and recognize me or anything else. I tried to squeeze her hand, and there just wasn't any return.

DR. NEMIROFF: So you remember those last days when it was difficult to get in touch with her.

Patient: If I could just see her the way she was before, you know, it would be all right, but I just get this vision of her the way she was when she died.

DR. NEMIROFF: That may be something to work on, getting in touch with those previous memories. How about your dad? I understand he died before your mother did.

Patient: He died in 1969, yes. He had cancer of the stomach. He was up at the Z VA Hospital.

DR. NEMIROFF: Uh huh. He was at the Z VA Hospital. Did you visit him there?

Patient: Yeah.

DR. NEMIROFF: And could you tell me a little bit about his funeral? Did he have a funeral?

Patient: Yeah, well, we didn't have any graveside service for him. He was cremated too. But we had a chapel service for him, and the VFW showed up in full force, but uh, I could never go and look at him in the funeral room.

DR. NEMIROFF: You didn't want to do that. Why not?

Patient: I didn't want to see him then. I'd never seen anybody before that was dead.

DR. NEMIROFF: I see. Did you cry during his service? Were you able to?

Patient: I don't remember. Some things don't stand out too clearly for me.

DR. NEMIROFF: Do you ever dream of your mother and father?

Patient: Oh, yes. I do.

DR. NEMIROFF: Uh huh. What do you dream of?

Patient: Well, I've had various dreams about them. One time I had a very shocking dream. I dreamed that my mother had the mind of a five-year-old. And that frightened me. I woke up crying that morning. It happened here in the hospital. I think that was the worst dream I've ever had.

DR. NEMIROFF: What frightened you about it?

Patient: The fact that she couldn't speak out or act like she had really done.

DR. NEMIROFF: Um hum—that she was helpless and actually couldn't be of help, theoretically couldn't be of help to you. Louise, I have one more very brief question. It's also of a personal nature, and this is going back to when you were 15. Sometimes some problems around that age come up when people have concerns about sexual matters of different sorts, and I was wondering whether you remember anything about that and how you feel about that.

Patient: My mother always sheltered me. She did too good a job of sheltering me, because the

idea of sex is frightening to me to a certain extent. I was brainwashed very well when I was young.

DR. NEMIROFF: I see. Could you just give me a notion of that brainwashing?

Patient: Well, she always told me that sex was something that happened between two people and was for the woman to become pregnant and have children.

DR. NEMIROFF: I see. Well, maybe that's something you can go into with Dr. Atkinson and understand a little bit more. We have to stop in a moment or two. Is there anything about your hospitalization or the interview this morning that you'd like to ask me or anyone here about?

Patient: Well, I probably can't think of anything right now, but the minute I leave the room I'll probably think of about five or six things.

DR. NEMIROFF: Great! Good! That means that we've had a good time this morning and we worked on things successfully if you do think of those five or six things. And I want you to remember every one of them and ask your doctor, OK? Is that a promise?

Patient: OK.

DR. NEMIROFF: You did really well this morning, and thank you so much for coming in.

Patient: Thank you for having me.

DR. NEMIROFF: Good Luck, Louise.

(The patient was escorted from the room.)

MS. KATHLEEN PORTER:* In the months I saw Mrs. Jackson in the outpatient clinic I tried to use Bruch's[1] model to deal with her feelings of total ineffectuality in terms of her emotions and the way she dealt with the people in her life. She did pretty well with that. In nearly four months she lost only about 10 pounds. Then her roommate got sicker, and (this is my analysis of it) they got involved in a game about who could be the sicker. I saw this as a replay of the situation with her mother: "Who is going to meet whose needs?" She lost 10 pounds in the two and a half weeks before admission.

DR. NEMIROFF: Was she in touch with her feelings about the roommate getting sick and having to care for the roommate, and having needs herself that weren't being met?

MS. PORTER: She was totally out of touch with how she felt about anything. She couldn't tell Dr. Atkinson or me about how angry she was at us about the behavior modification program we tried on the ward. Now she is able to say that she didn't like the restrictions and was angry, but at the time she only acted it out.

DR. NEMIROFF: I was impressed with the fact that she is now able to say a few angry things about her mother—to say that she feels her mother cheated her.

MS. PORTER: She's really getting more in touch with how she feels about that and about us, more able to identify her angry feelings. We've been trying to help her be more accurate and honest in expressing her feelings. The nurses on the ward also tell her when she is communicating effectively and when she's not.

DR. ROBBINS:† The first thing I'd like to say about anorexia nervosa is that it isn't a disease. It's a syndrome that is found in several different disease entities—unlike psychological malnutrition, which occurs in catatonic schizophrenia, mental retardation, schizophrenic decompensation or hunger strikes. For many years the standard text has been a book by Bliss and Branch.[2] Their definition of anorexia nervosa is "any psychologically determined weight loss of 25 pounds in a prescribed period of time." To me this is too inclusive; I prefer to describe anorexia nervosa as a syndrome in which there is emaciation and weight loss characterized by a psychologically determined reduction in nutritional intake.

The age of onset is puberty or post-puberty adolescence. More than 90 percent of anorectic patients are female. There is usually spontaneous or self-induced vomiting. There is almost always amenorrhea, as well as constipation, with excessive use of laxatives. Such patients are usually full of energy and even hyperactive, quite the opposite of what you would expect in someone that malnourished. Often there is not a real loss of appetite; hunger is defended against. In some instances there is poor awareness of hunger. Other fairly common behaviors in anorectic patients are stealing (often of food), a pre-occupation with food (gathering recipes, memorizing menus), and extreme sexual inhibition. Additional physical symptoms include decreased body temperature, heart rate, respiratory rate, and basal metabolism rate. The 17 ketosteroids are either normal or elevated,

*Kathleen Porter, RN, MS, Clinical Specialist, U.S. Veterans Administration.

†Alvin Robbins, MD, Assistant Clinical Professor of Psychiatry.

the opposite of what you might expect. The nails are brittle, and the teeth often loose. Occasionally you see avitaminosis and edema. In the later phases, with the cachexia, there is the onset of intercurrent illness, like tuberculosis or pneumonia, which is often fatal.

The two major authors to whom I would refer you are Mara Selvini Palazzoli[3] and Brunhilde Bruch.[1] They write of two kinds of anorexia nervosa. The atypical kind involves a situation in which the food itself has symbolic meaning; for example, oral impregnation and other hysterical fantasies. Other atypical cases might involve the inhibition of envy and jealousy, in which the prohibition of food is a way of dealing with envy, oral greed, and the like. Food may be seen as poison by severely paranoid patients and be refused simply because to eat it would be fatal.

The psychogenesis of typical or primary anorexia nervosa involves early and severe disruption of mother-child object ties, and the rejection of food is a defensive attempt to maintain identity and separation from a destructive, intrusive mother. Obviously a child's relationship to mother is geared around food. Mother and food are often equated when a child hasn't the ability to distinguish between them, and in the phase in which the child is developing independence and autonomy there is often a hassle about eating habits. Moreover, this often comes up during toilet training, and the constipation, enemas, laxatives and manipulative behavior are also part of it.

In Palazzoli's description of the psychogenesis, typically the mother is aggressive, hyperprotective, and incapable of considering the daughter a person in her own right. Her feeding of the infant is ritualized and controlled. In the daughter's childhood the mother interferes, criticizes, takes over vital experiences and prevents her daughter from feeling like her own person. All spontaneous and unique experiences are disqualified. It's almost as if the mother takes control of the girl's body and directs it, and what the girl is left with is something inside that body, her self. A split occurs between body and self: "My body belongs to mother; my self belongs to me." Here we have Bruch's ideas of conceptual and perceptual distortion in bodily image and Palazzoli's idea of bodily mistrust.

The onset of adolescence is often accompanied by feelings of helplessness and unreality. Sometimes depression, which decreases the appetite, brings attention to food, and may provide the nidus for the defense. Struggles against being captive, invaded, and exploited, with no life of her own, are the *sine qua non* of the anorectic patient. Starving gives her a sense of identity, control, and effectiveness. Her feeling is that the body, which is equated with the bad object, mother, would be overpowering if it were nourished. The body is a thing that grows at the expense of the person, and the struggle is to be a person, not a thing. The primitive quality of the object relationship is obvious. It isn't surprising that on MMPI's and especially on Rorschach tests most of these patients fall under the rubric of core schizophrenic.

Frequently the underlying cause of the anorexia is discovered to be severe affective disorder. In many instances the anorexia nervosa seems to be a defense against schizophrenia on the one hand and severe depression on the other. The body is something between "not me" and "bad me." If the defense works the absolute schizophrenic break is avoided because projection doesn't occur onto some other object but onto one's own body. Anorexia can avoid depression and suicide because the body needn't be destroyed as long as it is kept in check. I guess it is irrelevant whether or not you accept this theory of the dynamics. The point is: don't deal with this as a disease entity unto itself; understand that it is a series of defenses against severe ruptures in object relationships.

The patient presented today has a classic history. Her mother is described as insistent, controlling, demanding and intermittently loving. She restricted the patient's dating and sexual activity, even had her marriage annulled. The patient lived with her mother because mother decided it was best for her. We have the history of the onset of the problem in adolescence, with the absence of father, who I imagine was seen as a benign figure with whom the patient might ally against the mother. The chloral hydrate ingestion doesn't seem like a serious suicide attempt; with the mother right there it seems more like an expression of anger. Louise's long history of difficulty with object relationships, her repeated hospitalizations, and the results of her psychological testing indicate serious underlying depressive disorder.

Freedman and Kaplan[4] describe psychotic depressive reaction this way: sadness, energy depletion, weight loss, constipation, sleep disturbance, headaches, delusions of sin, guilt, and unworthiness, occasional suicidal thoughts, paranoid features, auditory hallucinations and hypochondria-

sis. It all fits. I see this patient's anorexia nervosa as a defense against her early aberrant object relationships, depression and psychosis. The problems that have occurred on the ward seem to repeat the early problems with her mother. She struggles for control to achieve some identity. She attaches herself to protective males on the ward, as she may have tried to do with her father to protect herself from her intrusive mother. The staff on the ward are saying EAT! She can understand intellectually that she's starving herself, but she needs *not* to eat to maintain a sense of identity. I think the therapeutic-administrative split fits right into her defense, and I suspect she made this split between good object and bad object absolutely necessary. As therapists you're in a double bind: you want her to eat because if she doesn't she's going to die—but if you insist that she eat you're repeating the earlier experience with her mother. So what do you do? I can mention what's been tried elsewhere.

If there were some hormonal deficit it was once thought that hormone therapy would take care of the anorexia. There wasn't, and it didn't. Insulin has been tried to stimulate hunger, but the results were equivocal. Chlorpromazine has been used. Electroconvulsive therapy (ECT) has been tried. Supportive therapy and analytic therapy have been successful occasionally. Behavioral therapy has been used to some advantage. Albert Stunkard[5] at the University of Pennslyvania focuses on the hypomanic, hyperactive quality in the anorectic patient. For every half pound gained per day he gives a patient a six-hour pass outside the hospital. Apparently this works in some cases. He's also tried giving such patients chlorpromazine hydrochloride (Thorazine®), which they hate because it slows them down, then decreasing the dose for increments in weight gain. The point is that in any behavioral therapy you have to find some wedge with the patient, something she wants.

I think any form of treatment stands a greater chance of success if you pay attention to the underlying cause of the anorexia nervosa. One treatment is going to look better than another only if it is more appropriate for the underlying illness involved. In this case I would suggest that the therapeutic-administrative split is not indicated because Louise needs to learn that the person saying EAT can also be non-invasive and non-destructive. This might be easier to learn from one person. The chances are that this patient will regain weight, go back out, find some other problem, and get herself back into the hospital. At that point I would recommend a trial of phenothiazine or antidepressant medication, and if that didn't work I would consider electroconvulsive therapy because I see her problem as an underlyng psychotic depressive reaction.

DR. DANIEL KRIPKE:* I agree that the risk of future episodes in this patient is enormous. A recent article by Prien et al[6] shows that both lithium and imipramine were effective in preventing depression. Perhaps she would benefit from either a tricyclic antidepressant or lithium to combat future episodes.

DR. LEIGHTON HUEY:† I can't be entirely complacent about viewing this as a syndrome and not a disease. Endocrinologists have been trying to document it as a disease entity, focusing on the fact that amenorrhea frequently precedes the onset of weight loss. They may yet find that we are dealing here with some malfunction of the hypothalamic pituitary axis.

DR. ROBBINS: Some cases we now call anorexia nervosa might have endocrinologic bases, but in many others every attempt to find hormonal deficits or organic difficulties has yielded nothing.

DR. CLEVELAND:‡ What interests me most is how you treat a patient who comes in weighing 60 pounds, won't eat and rejects all therapeutic attempts. When a patient is medically in danger from her anorexia, you have to *do* something. Thoma[7] has achieved good initial weight gain with tube feeding and high doses of chlorpromazine. He uses psychotherapy only when the patient is almost up to normal weight, if at all. Dally and Sargant[8] have successfully treated a series of patients with a combination of chlorpromazine and insulin in the acute stage, followed by a great deal of psychotherapy. Tec[9] has reported that nandrolone, an anabolic steroid, helped ten of twelve anorectic patients he treated during the last decade. Benady[10] has reported that cyproheptadine hydrochloride (Periactin®) has increased weight gain in a couple of patients, although I can't explain an antihistamine's having this effect either. It is obvious that the medical approach has its limits. You can keep a tube down only so long, and you can use, say, chlorpromazine only so long

*Daniel Kripke, MD, Assistant Professor of Psychiatry.
†Leighton Huey, MD, Chief Resident in Psychiatry.
‡Kitty Cleveland, MD, Resident in Psychiatry.

because a lot of these patients rebel against sedation.

The behavior modifiers steer away from medical treatment if they can, but what they do varies a great deal. Some of them have tried deconditioning patients who have an apparent phobia of food or eating, with fairly good effects on initial weight gain, but there are no good long follow-ups. In the follow-ups of five of Stunkard's patients I found that one committed suicide, and two continued very poor social adjustment; I wasn't impressed with those long-term results.

Laboucarie and Barres[11] have published a study of 39 patients with whom they tried ECT and achieved variable results. These were not psychotic patients, and I suspect that the efficacy of the treatment was related to the underlying cause of their anorexia, as Dr. Robbins has suggested.

In my opinion the best long-term treatment is psychotherapy. Most people agree that the classic analytic approach does not work with anorectic patients. Even Thoma,[7] who has an analytic orientation, says you have to form a very good alliance with the patient initially. In other words, you throw away the analytic handbook until you have the patient's confidence. Bruch[1] emphasizes that you must make the patient participate. You can't sit there interpreting, telling her what she feels. You must allow her to make her own interpretations, to come into contact with her own feelings, or hunger, or anxiety, and to realize that they originate in her body and are a part of her, not something imposed on her by the outside, mothering, figure.

DR. IGOR GRANT:* At Pennsylvania we noticed that anorectic patients often had distorted bodily images of themselves. At one time Dr. Stunkard had large mirrors on the ward, and he would say to a patient, "Please describe yourself." Amazingly, even the most emaciated patients would say, "Well, my breasts are a little bit too big. I have a little bit too much fat here on my hips." Also, I would like to underscore the statement that many of these patients really are not aware of their internal states, especially their hunger. This fits with the dynamic factor Dr. Robbins spoke of —the situation in which the mother has usurped the function of the child's internal sensing apparatus. I suspect there are similar factors in the background of some obese patients, who also don't seem well attuned to their inner states.

*Igor Grant, MD, Assistant Professor of Psychiatry.

The therapy at Pennsylvania was broader, I think, than the impression we have so far today. Dr. Stunkard avoided saying EAT by gearing the contract to weight gain and specific things that the patient obviously wanted. How the patient gained weight was in a sense immaterial—eating was not mentioned. Too, the antidepressants and phenothiazines were used differentially for patients who were thought to be primarily depressed or primarily schizophrenic. This regimen did work well in the hospital, but the patients tended to decompensate after discharge. When I left, family therapy was being tried in the treatment of younger patients.

DR. KENNETH MINKOFF:† When I was in Philadelphia I had a chance to observe a couple of sessions of that family therapy. The initial goal of the therapist was to intercede between the mother and daughter so that they were forced to relate to each other through him. Then he told the girl that she had to do without food completely to control her anorexia. She became negativistic about this prohibition, and began to demand food. He forbade any food except dry toast initially. Then she begged, increasingly frantically, and in the process expressed a lot of her angry feelings. Gradually he let her add items to her diet. Eventually he was able, quite casually, to tell her she could eat anything she wished.

DR. DANIEL BRUMFIELD:‡ I had the opportunity to test a 19-year-old anorectic girl on the bicycle aerodometer. Although she stood 5 feet 6 inches and weighted 89 pounds, she worked at loads at which the average girl or 40-year-old businessman would work, and she tolerated them much better. Her blood pressure rose less; her pulse rate rose less; and her recovery was fantastic. Her subjective experience was less troubled. I was impressed with how well she functioned and how good she looked.

DR. MINKOFF: I recall that some of Stunkard's patients registered up to 10 miles a day on the pedometers he had attached to their ankles. As they got better, the amount of activity decreased.

DR. GRANT: In view of all that energy, you need to be careful in designing your behavioral modification paradigm—gearing it to something like miles per day would be better than gearing it to something easily achieved.

†Kenneth Minkoff, MD, Resident in Psychiatry.
‡Daniel Brumfield, MD, Resident in Psychiatry.

DR. ROBBINS: This reminds me of a 12-year-old anorectic boy described to me by a local analyst several years ago. The boy had various neurotic fantasies and made a great to-do about food and recipes, but he wouldn't eat. In desperation the analyst took the boy's bicycle away, and the anorexia was cured almost immediately.

DR. HUEY: What about the sex distribution—the nine to one split?

DR. ROBBINS: If, as in the formulation I gave, the body were seen as separate from the self, as belonging to the mother, when a girl entered puberty and became physically like her mother, the bodily introject would fit, and the perceived need to defend the self against it would be reinforced. Boys would not experience this kind of reinforcement at puberty. The anorectic boy I described had oral impregnation fantasies that occurred around puberty and the birth of a sibling. No single dynamic factor has been established, although Bruch[1] does address the problem.

DR. NEMIROFF: It seems to me that in our contacts with an anorectic patient we need to avoid the power struggle that comes out of the background. Whether we use drugs, or behavior modification, or psychotherapy with the individual or her family, we need to work toward a therapeutic alliance with the hope of getting to those early aggressions, showing where they come from, and helping the patient work through them. I was very impressed that you have made a fine start in that direction with Louise.

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Refer to: Wegener's granulomatosis—Medical Staff Conference, University of California, San Francisco. West J Med 121:123-130, Aug 1974

Wegener's Granulomatosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been a tradition at this institution to ask our chief medical residents to present the Medical Staff Conference before their departure. Today Dr. David S. Gullion will discuss Wegener's granulomatosis.*

DR. GULLION:† Wegener's granulomatosis is a curious clinical-pathological complex of unknown cause. In 1931, Klinger[1] reported a patient who died in uremia with severe destructive sinusitis, nephritis and disseminated vasculitis. The anatomical pathologic features were particularly interesting in that they included numerous splenic granulomata, generalized arteritis and a glomerular lesion. A few years later, Wegener[2] reviewed three cases and was able to define this disease as a distinct clinical and pathological entity. He held the view that it was probably a unique variety of periarteritis nodosa. Because nasal involvement was present in most of his patients, he coined the phrase "rhinogenic granuloma."

Interest in this disease was revived almost twenty years later at Columbia University in the Departments of Medicine and Surgical Pathology. Godman and Churg[3] presented data from seven additional patients and established the pathological criteria for Wegener's granulomatosis. In conjunction with their publication, Fahey[4] presented the clinical aspects of the disease. These investigators emphasized that it is a distinct syndrome that is well characterized both clinically and anatomically. Clinically, the diagnosis may be suggested by a recurrent respiratory tract inflammation, particularly when associated with renal abnormalities. The pathological findings were consistent and allowed the establishment of certain criteria: (1) necrotizing granulomatous lesions in the upper air passages (nose, paranasal sinuses, nasopharynx, glottis, or adjacent regions) or in the lower respiratory tract (trachea, bronchi, lungs) or in both; (2) generalized focal necrotizing vasculitis, involving both arteries and veins, almost always in the lungs, and more or less widely disseminated in other sites; and (3) glomerulitis, characterized by necrosis (and thrombosis) of loops or lobes of the capillary tuft, capillary adhesions, and evolution as a granulomatous lesion.[3]

Some interesting characteristics of their patients were noted: severe destructive necrosis of the larynx and nasal and paranasal structures; coagulative necrosis of the spleen, which often was enlarged; aseptic necrosis of two-thirds of the mitral

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†David S. Gullion, MD, Chief Resident in Medicine.

Figure 1.—Necrosis and infection of lung in Wegener's granulomatosis.

Figure 2.—Microscopic picture of caseating granulomatous tissue demonstrating a granuloma (G), necrosis (N) and vasculitis (V).

valve leaflet and chordae; involvement of the coronary arteries with severe arteritis and, in all cases, involvement of the kidneys which showed characteristic fine punctate hemorrhages on the surface and glomerulitis on microscopic evaluation.

Some of these findings are reviewed in the figures. Figure 1 shows the gross anatomical picture of the disease in the lung. Noticeable are the large areas of necrosis and inflammatory masses which are numerous and frequently near the pleura. The necrotic aspects are well demonstrated by circumscribed white-yellow lesions. The center of these nodules is usually soft, friable and varies from reddish-yellow to greenish-brown. The large area of infarction, which is hemorrhagic, was most likely caused by the occlusion of pulmonary arteries supplying the area. In Figure 2 with the aid of a microscope we see through an area of necrotic, caseating, granulomatous tissue. Present are swirls of epithelial cells which are typical of granuloma formation. Figure 3 shows the acute necrotizing arteritis which is present in the pulmonary arteries. The artery shown is relatively large, but small arteries are more consistently involved in this process. We can see infiltration of the media by numerous mononuclear cells, and with an elastic stain one can observe disruption of the normal elastic structures of the arterial wall. A consistent pathological finding in the cases presented in the literature has been involvement of the pulmonary arteries.

The kidneys, as already mentioned, showed fine punctate hemorrhages on the surface. Viewed microscopically there was a characteristic focal necrotizing glomerulitis with fibrin thrombi and focal necrosis of glomerular tufts. Figure 4 shows a typical granuloma within the medullary portion of the kidney.

Differential Diagnosis

As will be discussed later, Wegener's granulomatosis presents in a variety of ways. These range from a very limited form to the overwhelmingly fulminant vasculitis with death in uremia. In the recent review by Fauci and Wolff,[5] the range of differentiation extended from diseases that are predominantly vasculitic to those that are definitely granulomatous. Classic periarteritis nodosa is a widespread vasculitis which is usually confined to medium-sized arteries and predominantly involves the bifurcation or branching of those arteries. The distal smaller vessels are usually only involved by extension or because of thrombosis. Otherwise, in periarteritis nodosa the small arteries and veins are spared, in contrast to the findings in Wegener's granulomatosis. There is renal damage in periarteritis, but usually not the focal necrotizing glomerulitis seen in Wegener's granulomatosis. Similarly, hypertension, which is so common in periarteritis, is rarely seen in Wegener's granulomatosis. Pulmonary vasculitis is uncommon in periarteritis nodosa (PAN) but, as mentioned, was found in every reported case of Wegener's. The systemic pulmonary arteries, namely bronchial vessels, however, are involved with the diffuse vasculitis in PAN. Finally, necrotizing granulomata are not a feature of periarteritis.

Moving away from the classic periarteritis, we have the microscopic form of periarteritis nodosa

Figure 3.—Acute necrotizing arteritis of pulmonary artery. Infiltration with mononuclear cells is shown.

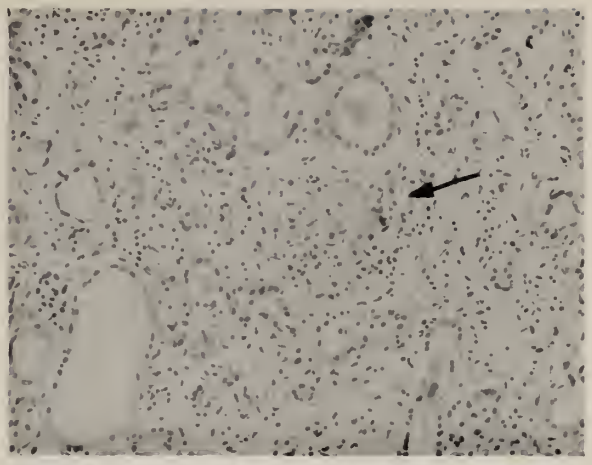

Figure 4.—Granuloma (arrow) in medullary portion of kidney from patient with Wegener's granulomatosis.

as described in the earlier literature, or what more recently has been designated by Zeek[6] as hypersensitivity angiitis. In the late 1940's and early 1950's Zeek described and reviewed hypersensitivity angiitis and periarteritis nodosa. Hypersensitivity angiitis is an acute necrotizing inflammation involving the small arterioles and veins, much as Wegener's granulomatosis does. The pulmonary vessels are frequently affected. The extravascular lesions in the spleen and kidney are also similar to those found in Wegener's granulomatosis. The differentiating point, however, is a frequent history of drug antigen being introduced shortly before the onset of symptoms. Most patients with this condition have had allergic reactions to sulfonamides. Pathologically, the distinguishing feature here is that all of the lesions of hypersensitivity angiitis appear to be in the same stage of involvement, in contrast to Wegener's granulomatosis in which the lesions are a combination of acute vasculitides in all stages of healing. Furthermore, granulomatous formation with necrosis is not a feature of hypersensitivity angiitis.

Continuing through the list of predominantly vasculitic diseases, there is systemic lupus erythematosus, scleroderma, dermatomyositis, Sjögren's syndrome, rheumatoid arthritis with arteritis and giant cell arteritis. In none of these disease processes does one find the classic triad of necrotizing granulomata, vasculitis of the upper and lower respiratory tract, and glomerulitis. Thus far none of the studied cases that have satisfied the established criteria of Wegener's granulomatosis has shown an abnormal serological pattern. Thus, by this criterion, one can frequently distinguish these other vasculitides from Wegener's. In the cases studied there has been no appearance of lupus erythematosus cells, antibodies directed to native double stranded deoxyribonucleic acid (DNA), single stranded DNA, ribonucleic acid (RNA), or mixtures of DNA with the nuclear proteins. There also has not been a detectable antinuclear antibody that reacts with a combination of nuclear material including histones, DNA and other nuclear substances.

Henoch-Schönlein purpura is a syndrome, usually found in children and adolescents, that involves the joints, gastrointestinal tract and kidneys. There is often widespread purpura, which reflects the pathogenic process of damage to the endothelium of small vessels. The presentation frequently includes abdominal pain, nausea, vomiting, diarrhea and hemorrhage. The renal lesion is usually focal and does not progress to renal failure. Again, the phenomenon appears to be allergic in origin and the lesions are usually of the same crop.

Continuing in the differential diagnosis, there are other diseases which have mixed granulomatous and vasculitic properties. Churg and Strauss[7] described "allergic angiitis and granulomatosis." Included in this group is the characteristic clinical syndrome of asthma, fever and hypereosinophilia.[8] The anatomical findings were very similar to Wegener's granulomatosis but differed in that the patients had severe asthma, there was pronounced although not persistent peripheral eosinophilia, there was a strong tendency toward cardiac involvement, and the respiratory tract lesions were less extensive and less aggressive. A variety of diseases with pulmonary infiltrations and eosinophilia (the PIE syndromes) may have aspects similar to

TABLE 1.—*Clinical Characteristics of Patients with Wegener's Granulomatosis*

Male : Female	3 : 2
Age Range	3 mos. to 75 yrs.
Peak	4th to 5th decade
Mean	44 yrs.

Symptoms	*Percent Cases*
Previously healthy persons	
Rhinorrhea and sinus pain	94
Fever	80
Anorexia, weight loss	80
Cough	60
Chest pain	60
Arthralgia/arthritis	60/20
Skin lesions	50
Otitis media	40
Ocular lesions	40
Hemoptysis	20
Neurological symptoms	20-50

Wegener's but do not involve the kidney and do have eosinophilia, which is uncommonly seen in Wegener's granulomatosis.

The granulomatous diseases that must be included in the differential diagnosis include the infectious, as well as the noninfectious ones (or those granulomatous diseases for which causes have not been identified). We can briefly eliminate the infectious cause by either culturing or observing the organism, and corroborating the diagnosis by serological tests with or without positive cellular immunity to the infectious agent. These diseases include tuberculosis, histoplasmosis, blastomycosis, coccidioidomycosis, syphilis, tularemia and lymphogranuloma venereum.

Sarcoidosis, although involving the pulmonary structures, may be easily differentiated on pathological grounds because of the non-caseating or non-necrotic aspects of the granulomata and the absence of vasculitis. Berylliosis produces pulmonary lesions very similar to sarcoidosis, but there is no other widespread involvement such as is seen in Wegener's granulomatosis. Usually there is a history of exposure to beryllium. Last, within the granulomata group we have the very rare and unusual lethal midline granuloma.[9] This is a poorly understood entity with destructive lesions of the midline upper respiratory tract structures, especially the nose, sinuses, palate and pharynx. This entity has also been described as agnogenic progressive lethal granulomatous ulceration of the nose and face or granuloma gangraenescens. There definitely is overlap of this syndrome with Wegener's granulomatosis. Pathologically disseminated visceral granulomata are present, at times even with occasional necrotizing angiitis. Glomerulitis, however, was not found in any case, and none of the patients died in renal failure. Some feel lethal midline granuloma is a variant of Wegener's granulomatosis.

The first of other pulmonary renal syndromes is the well known Goodpasture's syndrome, which is characterized by pulmonary hemorrhage and glomerulonephritis. The pulmonary hemorrhage is probably the most striking phenomenon distinguishing Goodpasture's from Wegener's; 98 percent of patients with Goodpasture's present with pulmonary hemorrhage. In addition, the diagnosis can be firmly established by the finding of antiglomerular basement membrane antibodies by immunofluorescence in a renal biopsy specimen. The pulmonary lesions are thought to be a reaction of the anti-basement membrane antibody with those basement membranes of the alveolar septal membranes. On immunofluorescence a very fine linear deposit is seen. This linear deposition is due to the interaction of the basement membrane with the antibody itself as opposed to an immune complex glomerulonephritis in which the immune complexes are filtered at the glomerulus and appear as a coarse, granular deposit along the basement membrane. This type of deposition is not specific and, in fact, has also been found in a few cases of Wegener's granulomatosis. Streptococcal infections of the upper respiratory tract and pneumonia with glomerulonephritis can be differentiated on culture, as well as on serological grounds.

To complete the differential diagnosis, neoplastic diseases should be considered because of their location. Nasopharyngeal lymphoma and sarcomas, midline malignant reticulosis, primary metastatic lung disease, Hodgkin's disease and lymphoma involving the lung all may resemble Wegener's because of the granulomatous reaction and necrosis associated with the neoplastic tissue. A few reports in the literature have made note of so close a resemblance of the biopsy specimen seen in Wegener's to that in neoplasia that a diagnosis of Hodgkin's disease was seriously entertained. Some of the bizarre cells seen in Wegener's may resemble Reed-Sternberg cells or even those of a reticulum cell sarcoma.

Clinical Characteristics

The clinical characteristics of Wegener's granulomatosis are presented in Table 1. The ratio of males to females is about 3 to 2, and in Fauci's series it was 11 to 7. The age range of patients

is from three months to 75 years, with a peak incidence in the fourth and fifth decades and a mean age of 44 years. The typical clinical presentation is with discomfort or complaints referrable to the upper respiratory tract. The complaints may be those of severe rhinorrhea, a nasal mucosal ulceration and sinus pain or drainage. These symptoms often wax and wane over months to years before the more fulminant aspects of the disease appear. In fact, renal involvement before nasal or sinus complaints is particularly unusual. Associated with this may be the involvement of the pulmonary structures leading to cough, pleuritic chest pain, abnormal chest x-ray studies, and hemoptysis. The latter occurs in up to 22 percent of cases. The presenting signs and symptoms in patients may be varied but usually revolve around the respiratory tract. However, the patient may present with skin ulcerations, joint symptoms, ocular manifestations or recurrent middle ear problems. Anorexia, malaise, fever and weight loss are all constitutional symptoms which frequently are found early in the course of disease. The clinical presentation is varied, and as mentioned, overlaps many other diseases.

Systems Involved in Wegener's Granulomatosis

For an appreciation of the wide spectrum of disease I will present the system involvement and describe some of those abnormalities found in patients with Wegener's granulomatosis. The eyes may be involved in up to 40 percent of cases. The ocular lesions reported include corneo-scleral ulceration, necrogranulomatous keratitis, granulomatous sclero-uveitis and conjunctivitis with occasional proptosis and pseudotumor of the orbit. In a series at the National Institutes of Health,[5] conjunctivitis, episcleritis and corneal ulceration, retinal artery thrombosis and proptosis were seen, and one patient had severe scleromalacia perforans.

About one third of patients with Wegener's granulomatosis have ear involvement, usually manifest by recurrent middle ear inflammation and pain.

Cutaneous involvement has been reported in up to 50 percent of patients. The lesions usually seen are those associated with the thrombosis of arteries and necrotizing angiitis. This leads to necrosis and ulceration of the skin. Subcutaneous nodules have also been reported, as have necrotizing papules of the finger tips.

Muscle involvement is uncommon and usually seen only as a perivascular infiltration. True myositis has not been a feature of this disease.

There are frequent complaints of arthralgias, but true arthritis is not common. The joint symptoms are usually transient and do not play a major role in the presenting symptoms or in the overall course.

As was mentioned before, there is a report of necrosis of the mitral valve with infiltration of mononuclear cells without evidence of bacterial infection.[3] The involvement of the coronary arteries is not frequent but may be associated with life-threatening, refractory arrhythmias and actual myocardial infarction with necrosis. Occasionally pancarditis is seen. In the series of Fauci and Wolff,[5] the heart was involved in five of seventeen patients. Three had pericarditis and, of these, one died of pulmonary hemorrhage. Two other patients died of intractable arrhythmias, and the autopsy on one confirmed severe vasculitis of the anterior descending branch of the left coronary artery.

As with many other systemic diseases, the nervous system is involved in a significant proportion of cases of Wegener's granulomatosis—reports put the incidence between 25 and 50 percent. Drachman[10] described the lesions as being of three types: (1) contiguous involvement from a destructive granulomatous process of the sinuses which involved the orbit and surrounding structures; (2) remote granulomatous lesions of the meninges or intracerebrally; and (3) a more generalized vasculitis of the nervous system which may be clinically very similar to that seen in lupus erythematosus. Specifically, the vasculitis may be associated with cerebrovascular occlusions, intracerebral or subarachnoid hemorrhages, polyneuritis or a mononeuritis multiplex such as is seen in periarteritis nodosa. The mononeuritis multiplex is not an infrequent finding in this disorder.[11]

Respiratory tract involvement, as has been emphasized here, is a cardinal feature of Wegener's granulomatosis, and the diagnosis should probably not be made unless there is such involvement. Mucosal ulcerations, septal perforations, saddle nose deformities from the destruction of the cartilaginous and bony portion of the nose, and various degrees of sinusitis are the most common findings. Secondary bacterial infection may be present in more than half the patients with sinus involvement. The lungs are almost invariably involved,

Figure 5.—Pulmonary nodules in Wegener's granulomatosis.

Figure 6.—Lateral view showing pleural involvement by nodules.

but have no characteristic lesion. Commonly seen are solitary or multiple nodular densities (Figures 5 and 6), or ill-defined infiltrates (Figure 7) which may vary in size and characteristics, from small coin-like lesions to large bilateral infiltrates. The occurrence of cavitary formation is becoming more frequently reported, with thick-walled cavities being most common and usually accompanied by surrounding inflammatory reaction. However, thin-walled cavities, characteristic of coccidioidomycosis, may be seen in up to 30 percent of patients with cavities. The pulmonary symptoms vary but usually consist of a low-grade persistent cough and some mild chest discomfort or pleuritic pain. Occasionally they may be of a more severe nature, with fulminant respiratory failure.

Finally, the renal involvement is the dreaded complication in generalized Wegener's granulomatosis. The prognosis is grave when renal damage is present, and there is frequently rapid progression to death due to renal failure. The urinary abnormalities of proteinuria, hematuria and red-blood-cell casts may be present for a number of weeks, but once there is functional impairment, the renal disease does not spontaneously arrest or regress.[4] As was mentioned before, the most common finding is a focal necrotizing glomerulitis not unlike that seen in subacute bacterial endocarditis and certain forms of periarteritis nodosa. Associated with this glomerulitis are various stages of healing, including hyalinization, adhesions and crescent formation. As we shall discuss later, the greatest benefit of therapy is control of the progression of the renal lesion. The long-term survival is directly contingent upon the degree of renal impairment. Fortunately, hypertension is not a problem in patients with Wegener's granulomatosis and in the most recent review[5] was not found at all.

In 1966 Carrington and Liebow[12] described 16 patients with a limited form of Wegener's granulomatosis. There was frequent upper and lower respiratory inflammation with concomitant symptoms. Abnormal chest x-ray studies were found in all cases, frequently raising suspicion of a neoplasm. Systemic manifestations were present—weight loss, fever, malaise and accelerated erythrocyte sedimentation rate—as were extrapulmonary lesions. There have been further reports of the limited form of Wegener's granulomatosis and the characteristic finding is the absence of the renal damage.[12,13]

Laboratory Findings

There is nothing specific in laboratory findings to confirm or deny the diagnosis of Wegener's

Figure 7.—Bilateral nodular perihilar infiltrates.

TABLE 2.—*Types of Therapy Used in Treating Wegener's Granulomatosis*

Antibiotics
Radiotherapy
Adrenocorticoids

Cytotoxic Agents	*Toxicity*
1. Nitrogen mustard ..	Bone marrow depression
2. Methotrexate	Bone marrow depression; liver, GI, abnl.
3. Chlorambucil	Bone marrow depression
4. Azathioprine (1-2mg/kg/day) ..	Immunologic suppression Bone marow depression ↑Incidence malignant tumors
5. Cytoxan (1-2mg/kg/day) ..	Immunologic suppression Bone marow depression Incidence malignant tumors Hemorrhagic cystitis Azoospermia Ovarian destruction
Heparin (30-40,000 units/day)	Hemorrhagic complications

granulomatosis. Again, the combination of clinical, laboratory and pathological data must be used to make the diagnosis. Anemia is common; it is usually normocytic and normochromic without morphologic abnormality of red cells. Bone marrow examination usually shows only a mild erythroid hyperplasia without abnormal cells. Microangiopathic hemolytic anemia has been found in a few cases.[14] Its exact cause is unclear but most likely it is related to either splenic disruption of cells by fibrin strands or by the glomerular lesion which, at times, is associated with fibrin deposition with or without thrombosis of capillary tufts. Often there is a mild leukocytosis but specifically without eosinophilia. Interestingly, in the National Institutes of Health series,[5] seven out of eighteen patients had a platelet count greater than 400,000 per cu mm. There were no patients with platelet counts less than 150,000 per cu mm. There may be an acceleration of the sedimentation rate, and the mean value in the reported series is approximately 90 mm in one hour.

Treatment

The therapeutic approaches used in treating Wegener's granulomatosis have been many and varied (Table 2), probably owing to the uncertainty about what causes the tissue effects. None of the previous methods have been successful; and, therefore, the current approach in the management of patients with Wegener's granulomatosis is to treat the tissue inflammatory response and the immunological system which may be contributing to the pathogenesis in some as yet unknown way. Antibiotics were used consistently in the past few decades. When secondary infection occurred, as it did in approximately 40 percent of patients, antibiotics often were effective in reducing the acute infection. However, their use for treatment of underlying disease is not efficacious. Radiotherapy of local granulomatous lesions has been used often, and in some cases regression of the treated lesions has followed. However, one must keep in mind that regression may occasionally occur without treatment of any kind. Corticosteroids have been widely used in treating this disease. The effect has been unpredictable or unsuccessful, and renal involvement has progressed in all cases in spite of continued steroid therapy. The frustration with the therapy in Wegener's granulomatosis is attested by Fahey's seventh case.[4] After treatment with large doses of adrenocorticotropic hormone (ACTH) became less effective, "radiotherapy, thiethylene melamine, stilbesterol, testosterone and snake venom produced no change." Nitrogen mustard then was given, with a transient effect.

Because the prognosis of Wegener's granulomatosis is so poor, with an average life span of five months and mortality of 93 percent in two years,[15] there has been increasing interest in the use of cytotoxic agents in treatment. In 1954 and

during the following few years, nitrogen mustard was given a trial in some isolated patients. Following this, McIlvanie,[16] in 1966, reported upon a patient with the limited form of Wegener's granulomatosis who received chlorambucil with a successful response.

The following year Hollander and Manning[17] reported a case in which nitrogen mustard was given intravenously and then chlorambucil by mouth, with good response of a severe renal lesion. By 1971 there was increasing agreement that cytotoxic agents were beneficial in treating this disease, and increasing numbers of reports began to appear showing the efficacy of a variety of cytotoxic agents with emphasis on azathioprine and cyclophosphamide (Cytoxan®). Novack and Pearson[18] presented four patients who received cyclophosphamide (usually orally) with apparent regression of the lesions in all the patients. In these patients, steroids were either not used concomitantly or the doses of them were being tapered rapidly during the period of observation.

It is the current feeling of Fauci and Wolff[5] that cyclophosphamide or azathioprine should be started at the dose of 1 to 2 mg per kg of body weight per day by mouth and that the patient's clinical course should be monitored with frequent blood cell counts and renal function studies, including urinalysis. The institution of corticosteroid therapy at a dose of 40 to 60 mg of prednisone per day should be limited to those times when the constitutional symptoms or inflammatory vasculitic process are rampant. The two important toxic manifestations of cyclophosphamide need to be kept in mind: The hemorrhagic cystitis may occur either acutely or after many months of oral therapy. The bladder fibrosis and chronic inflammation is particularly disturbing. In addition, there is now increasing awareness of the effects of cyclophosphamide and other cytotoxic agents upon the reproductive organs, specifically, azoospermia and ovarian destruction.

I should mention two reports describing the use of heparin in the treatment of Wegener's granulomatosis. The rationale for its use originates from the fact that fibrin deposition in the glomerular capillary tufts is occasionally seen, with or without thrombosis. Roback[19] described a child with Wegener's granulomatosis who was treated with heparin and azathioprine. It was felt that the dramatic response of the renal insufficiency was due to the institution of heparin therapy. Likewise, Whitaker[20] presented a case of Wegener's granulomatosis with renal involvement that was treated with a combination of heparin and azathioprine with similar results.

In patients with the limited form of Wegener's granulomatosis the exact timing of therapy needs to be handled on an individual clinical basis. The pulmonary insufficiency may be of a great magnitude and require cytotoxic therapy. However, if the symptoms are low-grade and the disability not severe, the patient may not necessarily have an indication for cytotoxic therapy.

How long to continue therapy has not been established. As general outlines, it is necessary to keep in mind that with significant pulmonary and renal involvement the disease is uniformly fatal. If there is good control of the disease, then a one-year unequivocal remission would probably warrant tapering and stopping of therapy at that time. If the disease continues to smolder without definite remission, continued oral therapy may be indicated. The renal abnormalities should guide one as to the necessity of continued therapy.

Trade and Generic Name of Drug

Cytoxan® ..... cyclophosphamide

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Important Advances in Clinical Medicine

Epitomes of Progress— Physical Medicine and Rehabilitation

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Physical Medicine and Rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Physical Medicine and Rehabilitation which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Physical Medicine and Rehabilitation of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Treatment of Muscle Contusions in Athletes—A New Method

SLOWNESS OF RESOLUTION of muscle contusions in athletes has recently been carefully documented by Jackson and Feagin. Periods of disability from moderately severe to severe quadriceps contusions ranged from 28 to 180 days. Our experience with the customary methods of local heat, proteolytic enzymes and graded exercise has also shown the same slow course of recovery in injuries to the quadriceps, deltoid, hamstring and gastrocnemius.

An alternative method of early treatment consisting of temporary local anesthetic blockade of the peripheral nerve to the contused muscle has been used successfully in 32 athletes ranging in age from 20 to 45 years. The nerve was located easily by use of a peripheral nerve stimulator, whereby variable voltages could be applied through the tip of a coated Teflon® needle to the peripheral nerve. Prompt resolution of large contusions (or hemorrhages) was obtained with a single injection of 5 to 15 ml of 1 percent mepivacaine (Carbocaine®) in 27 patients. Five patients needed repeat blocks. Contusions were treated successfully in the quadriceps (18 patients), gastrocnemius (four patients), biceps brachii (four patients), hamstrings (four patients), and deltoid (two patients). A remarkable finding was the consistently small size of the underlying hemorrhagic area after the muscle had been suitably relaxed by blockade of its nerve.

It is postulated that nerve blocking permits easier venous or lymphatic emptying while the muscle is in diastole, and also reduces sympathetic vasoconstrictor influences on resistance and capacitance vessels. After temporary paralysis of lower extremity muscles, the patient was subjected to pneumatic pumping of the involved extremity, through a Jobst® inflated support. He was allowed

to walk promptly on crutches, and was ordinarily able to resume normal athletic activities within one to four days. No restrictions whatever were placed on the early use of the upper extremity muscles. Recurrence at the injured site did not occur, and there was no evidence of myositis ossificans in nine patients examined one year after injury.

WALTER J. TREANOR, MD

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Dantrolene Sodium in the Management of Spasticity

SPASTICITY THAT IS CAUSED by central nervous system involvement often induces contractures and deformities, limits the patient's capacity to care for himself, impairs gait, and makes personal hygiene and nursing care more difficult. The pharmacologic management of severe spasticity has continued to be relatively ineffective, even since the introduction of the so-called "muscle relaxants." In efforts to modify or abolish spasticity, clinicians have had to resort to various nonpharmacologic measures, such as chemical nerve and motor point blocks (alcohol, phenol), surgical tendon lengthenings and releases, rhizotomy, spinal cord hypothermia and, more recently, stereotaxic surgery.

Today, the pharmacologic agent most widely used for the treatment of spasticity is diazepam (Valium®); but this drug, since it is principally a centrally acting relaxant, seldom reduces severe spasticity without simultaneously sedating the patient to the degree that function is hindered rather than enhanced.

A peripherally acting skeletal muscle relaxant, dantrolene sodium (Dantrium®), was recently introduced. Thus far, comparative clinical and electrophysiological studies have indicated that it is more effective than diazepam in the treatment of spasticity. It has benefited some patients, though a number fail to respond to the new drug. Some patients seem to derive greater benefit from dantrolene and diazepam combined than from either drug alone. Consequently, before resorting to an irreversible nonpharmacologic procedure intended to modify or abolish spasticity, the clinician should consider a trial of dantrolene sodium. Side effects (the most common is general weakness) are usually transient, and may be minimized by starting with relatively small doses, that is, 25 mg twice daily, and increasing this in 25-mg increments until the adult patient is receiving 100 mg four times daily.

If dramatic change is anticipated, dantrolene may prove disappointing; but the drug does represent a new mode of action as a muscle relaxant in that it has a peripheral effect. Studies indicate that it uncouples excitation-contraction, probably by interfering with or inhibiting calcium release from within the sarcoplasmic retriculum of muscle. Neuropharmacologic advances may ultimately lead to the development of dantrolene-like compounds or derivatives that will prove to be more widely effective. The availability of such compounds would facilitate the pharmacologic management of these patients, and reduce the necessity to resort to nonpharmacologic measures to modify or abolish spasticity.

ALVIN GLASS, MD

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Intermittent Catheterization and Bladder Rehabilitation: Its Role in Spinal Cord Injury Patients

EARLY RESULTS of intermittent catheterization in patients with traumatic spinal cord lesions show considerable reduction in persistent urinary tract infection and pronounced reduction in other complications, including vesico-ureteral reflux, hydronephrosis, pyelonephritis, calculous disease, penoscrotal abscesses and fistulas.

A study was done at VA Hospital and Baylor College of Medicine, Houston, Texas on 117 patients in whom Foley indwelling catheters were placed for periods of less than three weeks to more than five years. After a detailed urological work-up, these patients were put on a program of intermittent catheterization including self-catherization in paraplegics. At first, the catheterizations were done every four hours, day and night, until some spontaneous voiding (bladder triggering) was noticed. The schedule then was changed to every

six hours. The frequency of catheterization was gradually reduced with increasing spontaneous voiding. The procedure was stopped when the residual urine was less than 150 ml. The period of intermittent catheterization varied from 39 to 138 days (mean 79 days) in acute patients and 3 to 25 days in chronic patients. A separate program was used for acute and chronic patients. The patient's profile of fluid balance and urinary culture was done before the start of intermittent catheterization. All catheterization was done aseptically by paramedical personnel and all paraplegic patients were trained to catheterize themselves. The role of bethanechol chloride as a bladder assist for decreasing period of intermittent catheterization has also been evaluated. Optimal dosage which halved the period of catheterization has also been established. Almost all patients with Foley indwelling catheters at the start of intermittent catheterization were infected; however, after intermittent catheterization about 75 percent were infection free. Overall 92 percent catheter-free status was achieved without operation on the bladder neck. One of the important goals was to do minimal operation, and a conservative bladder neck sphincterotomy to avoid incontinence has been advocated. Such an operation was done on six patients and the results improved to 98 percent catheter-free status.

INDER PERKASH, MD

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Treatment of the Frozen Shoulder

ADHESIVE CAPSULITIS of the shoulder is an established clinical entity associated with chronicity and numerous therapeutic regimens.

It is characterized by pain in the shoulder during the first three months, then loss of pain but persistent limitation of motion in the next three months. Spontaneous recovery is reported in 60 percent of patients.

Types of treatment vary: (1) orally administered medicine of the phenylbutazone series; (2) exercises, active and with avoidance of gravity during the painful "hot" period of the first three months with avoidance during this phase of vigorous or passive manipulative exercises; active assistive exercises during the subsequent painless "frozen" phase; (3) if arthrography shows a "cuff tear," orally administered anti-inflammatory agents and active exercises or (4) suprascapular nerve block combined with active exercises.

More recently, there have been encouraging results from local injection of depot corticosteroids in the supraspinatus tendon, biciptal tendon and capsular area given in a series. However, emphasis is still placed on pain relief and gradual regaining of the range of motion.

RENÉ CAILLIET, MD

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Fibrillation Potentials in Upper Motor Neuron Disease

CLINICAL ELECTROMYOGRAPHY (EMG) is a useful tool in helping to distinguish normal from abnormal functions of muscles. The finding of fibrillation potentials on EMG in patients with hemiplegia secondary to cerebrovascular accident was first reported in 1967. This finding was confirmed and the subject reviewed in a recent article by Kruger and Waylonis. Fibrillation potentials have also been reported in patients with upper motor neuron paralysis secondary to spinal cord injury. The possible explanation for the origin of these abnormal potentials in patients with upper motor neuron disease is discussed in the recent article by Taylor, Kewalramani and Fowler.

Fibrillation potentials are probably the most common and certainly the easiest to recognize of the abnormal potentials observed in clinical EMG. Early clinical studies plus experimental studies with animals and man led to the concept that fibrillation potentials are characteristic of (lower motor neuron) denervation. As a result, the term fibrillation potential has become synonomous with "denervation" in clinical practice. In light of the above reports of fibrillation potentials in patients with upper motor neuron disease, plus the experimental studies by Josefsson and Thesleff demonstrating that fibrillation potentials occur in experimental animals when release of acetylcholine is blocked with botulinus toxin, the concept that fibrillation potentials are synonomous with dener-

vation is no longer acceptable. They have also been described in myopathic diseases as well as in the conditions described here.

The significance of these findings is that the practice of using the word "denervation" or "denervation potentials" in the EMG report to indicate that fibrillation potentials were observed should be discouraged. The fact that fibrillation potentials are always abnormal is not questioned, however, we should report only that fibrillation potentials were found and the pattern or distribution in which they were found. The final conclusion as to whether or not they represent denervation is based on: (1) the distribution of the abnormal findings, (2) the characteristics of the voluntary potentials, and (3) clinical observations.

ROBERT G. TAYLOR, MD

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Treatment for Bell's Palsy

IN THE MANAGEMENT of Bell's palsy there is controversy as to (1) reliable assessment of prognosis and (2) effectiveness of proposed "curative" treatment regimens. To place these issues in proper perspective, one must understand three variations of the natural course of the process. The majority of patients (65 to 85 percent) *recover fully* within a few weeks to approximately two months *without therapeutic intervention.* Of the remaining patients, approximately one-half experience partial nerve regeneration which delays adequate recovery to between two and six months. The remainder, or approximately ten percent of the total number, experience either slow recovery or else a recovery that is cosmetically unsatisfactory because nerve regeneration is insufficient to restore the denervated muscle fibers.

Valid criteria for assessing prognosis and actual degree of risk of nerve degeneration should be the basis for selecting patients for "curative" treatment. This would avoid treating many persons unnecessarily and would be effective in protecting those at greatest risk from unsatisfactory cosmetic results.

One method of selection being studied is the use of electromyography to distinguish partially paralyzed from totally paralyzed facial muscles. Daily examination after onset serves to define the completeness of the palsy during the process and hence the risk of nerve degeneration. Additionally, response to high-dose prednisone or any other treatment is noted day to day as a measure of effectiveness.

CARL V. GRANGER, MD

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New Prosthetic Appliance

A NEW DEVICE called the modular above-knee prosthetic appliance has been developed at Bellevue Hospital, New York City. It consists of an above-knee prosthetic attachment with a quadrilateral socket that contains an inflatable plastic pad to accommodate immediate post-operative fitting of any stump. This modular device has the advantage of avoiding undue delay in ambulation for a debilitated geriatric patient while waiting for the preparation of a conventional prosthetic limb. It provides a well-fitting socket to assure comfort; it can be mass produced and the "modular" component may be shipped to remote areas where prosthetists are not available.

GREGORY BARD, MD

REFERENCE

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PICA Test for Aphasia

APHASIA RESULTING from a cerebral vascular accident may cause considerable frustration and depression for the patient, as well as for the family. In the past, instruments to evaluate the disability, to predict recovery and to assess progress were imprecise, tended to be subjective and were difficult to interpret. Furthermore, it was difficult to determine when the patient had reached his maximum potential.

The Porch Index of Communicative Ability

(PICA), developed by Bruce Porch, PhD, overcomes these weaknesses. This test has been standardized and validated, and its reliability has been established. Administration of the test yields results which can be used as a guide for therapy, to measure progress from month to month and to graphically show when maximum potential has been reached and stabilized. Approximately forty hours of training are necessary to administer the test.

The limitations of the PICA are that it cannot be used with children nor with high level aphasics. A corresponding vehicle for children is now being developed.

SETH DOUTHETT, MD

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Low Back Pain

SINCE MIXTER AND BARR postulated that lumbar disc herniation is the predominant cause of low back pain with and without radiation to the leg, other causes have been neglected or minimized. Recently there has been renewed interest and research emphasizing the importance of the posterior facets as the site of back pain with radiation to the leg.

The innervation of the posterior facets has not been confirmed to verify that each facet has a double nerve supply. The nerves to the facets are the articular branches of the posterior primary division of the segmental root of the ipsilateral side.

It has been reported that rhizotomy of these nerves relieves pain. Recent improvement in facet arthrography has made it possible to make sure the injection is made into the joint. Injecting irritative substances into these joints has reproduced lumbar pain and caused referred pain into the buttocks and posterior back. Relief of pain has been afforded by instilling steroid or an analgesic into the facet. A new era of understanding of new mechanisms of lumbar radicular disabling pain appears to be imminent.

RENÉ CAILLIET, MD

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EDITORIAL

Critical Masses in the Distribution of Health Care Services

THE PROBLEM of providing better access to health care for all citizens has occupied the attention of planners in government and elsewhere for more than a decade. Much of this attention has been focussed on the number and distribution of physicians. It was assumed that if the number of physicians were increased, a surfeit would surely result in better distribution particularly to underserved areas and perhaps would lower fees as well. And there were other assumptions. If the ethnic minorities were better represented in the profession, this would lead to more and better care for minorities. And since most physicians who practice now consider themselves specialists of one sort or another, it was assumed that a forced draft production of "family physicians" to render "primary care" was needed.

While there is something to be said for each of these assumptions, there is also good evidence that they are something less than completely valid. For instance, physicians are known to thrive in areas of high physician density. They do not flee them. Physicians of ethnic minorities do not always rush back to the ghettos from which they have escaped by dint of their hard work, although some do. And there can never be enough "family physicians" produced, in the present mold at least, to care for more than a fraction of the demand for primary care. Fortunately, many if not most specialists will continue to render more or less primary care just as they have in the past.

If it is true that the assumptions upon which the quite massive effort to improve the distribution of physicians and with them health care services are wrong, then it may be predicted that the effort will fail. Since this may well be the case, other approaches should be sought. It is suggested that certain characteristics of the health care system itself and certain human factors may deserve more attention than they have received.

It is fashionable, particularly among planners, to say that there is no health care system or that it is a non-system. The fact is, there is a health care system, it is quite complex and actually quite efficient and it is the instrument within which physicians must bring medical science and medical art to bear upon the troubles of their patients. A most important element of the system is the interaction among physicians which occurs within it. This interaction is essential to assure physician satisfaction, a high standard of practice, continuing professional competence, and ready access to any and all of the resources of the system which may be needed in patient care. Today's physicians will not, indeed they cannot, practice in physical or intellectual isolation from this system, and it is foolish to expect them to do so.

Human factors also deserve more attention than they have received. Today's physicians live in an era of social progress. They are fully aware that plumbers, electricians and airplane pilots earn as much or more than many physicians for a comparable number of hours worked. It is only human that the incentives to assume responsibility for patient care around the clock, seven days a week have somewhat lessened. Other equally human factors include the life styles of persons of the intellect and education of physicians, and their needs and the needs of their families for educational and cultural fulfillment. It is a fact that the opportunities for such fulfillment are apt to be poor or lacking in the urban and rural areas now underserved by physicians.

The problem, then, is to extend the health care

system itself in such a way that it will meet the needs of underserved areas. Neither the characteristics of the system, nor the human needs of the persons serving or to be served, nor the cultural or geographical remoteness of the areas to be served are to be ignored. Some kind of a mix of personnel and resources has to be achieved for each underserved area.

It is suggested that a concept of critical masses might be a useful device to accomplish the above. A critical mass could be defined as the minimum mix of the essential components needed to make a reaction go spontaneously or to make a service viable under the given conditions. Such an approach would make possible the introduction of all pertinent professional, physical, human and cultural factors in appropriate amounts and combinations to assure viability. The concept could be applied at any level of the health care system. The goal would be to plan so as to assure viability for the segment of the health care system in relationship to the system as a whole.

If the time has come to develop a more sophisticated, more realistic and more human approach to planning for the better distribution of health care services, the critical mass approach would seem to be a possibility worth exploring.

—MSMW

Gallium-67: Broad Spectrum Diagnostic?

THE GLORIOUS EXPECTATIONS for gallium-67 (^{67}Ga) as a tumor-imaging agent have been tarnished in part by its lack of specificity. Investigators in search of a "silver bullet" for detection of neoplasia were dismayed to find ^{67}Ga-citrate localizing in such oncologically disinteresting places as abscesses and recent surgical incisions. It remained for a small group of relatively broad-minded investigators to attempt to exploit this lack of specificity.

^{67}Ga-citrate does localize consistently in areas of inflammation due to infection. This aspect of ^{67}Ga has been well known in the nuclear medicine community for many years. Published documentation of such findings was made by Lavender et al in reporting ^{67}Ga uptake in one breast and one lung abscess,[1] and also by Lomas et al in a later publication noting ^{67}Ga uptake in hepatic abscesses.[2] Unpublished documentation abounds. However, the significance of these findings was never fully appreciated.

The thought of using ^{67}Ga specifically for imaging inflammatory lesions was first advocated by Lomas et al,[3] who found ^{67}Ga highly useful in the detection of empyema of the gallbladder. More recently, Littenberg and associates from San Diego have advocated the general use of ^{67}Ga-citrate for diagnosis of occult abscesses in patients with sepsis. Interestingly, one of their patients had pyelonephritis and unilateral renal localization on the radiogallium scan.

The latest contribution by Kessler and his associates, published elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE is a logical progression of this theme. While the authors admonish at the outset that their results are preliminary, their interesting presentation cannot escape some criticism on scientific grounds. They present a technique they hope "may prove useful in differentiating between upper and lower tract infections," but they present no valid controls—that is, patients with only lower tract infections. If, in fact, it turns out that a significant portion of patients with lower urinary tract infections have positive scans, the utility of the technique for this application is open to serious question.

Beyond the merits of this specific application, however, the broader question remains. Is specificity really necessary in a diagnostic agent such as ^{67}Ga? We have learned to live quite well with brain scanning, lung scanning and bone scanning, all of which are outstandingly nonspecific. We accept the role of the scintigram in such instances to locate rather than to identify the disease process. There is no law (as yet) which restricts us from use of more specific procedures, once the location of the abnormality has been identified. So be it with ^{67}Ga-citrate.

PAUL B. HOFFER, MD
Director of Nuclear Medicine
Department of Radiology
University of Chicago,
Pritzker School of Medicine

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New Hope for an Old Ill — Anorexia Nervosa

ANOREXIA NERVOSA, the subject of the specialty conference in this issue of THE WESTERN JOURNAL OF MEDICINE, is now in the midst of another of the periodic bursts of interest which recurrently accord this rare and curious condition a prominence out of all proportion to its practical importance as a health problem. This time the interest arises from new forms of treatment which are, at the very least, better than the old, and potentially very much better. As has so often been the case in the past, these new treatments reflect the fashions of the times. They are psychopharmacology, behavior modification, and family therapy.

Effective treatment for anorexia nervosa is best divided into two quite distinct phases: short-term intervention to restore body weight and save the patient's life, and long-term treatment to ameliorate the often long-standing and pervasive personality problems. The first really effective measures for dealing with either phase—in this case short-term intervention — were introduced 15 years ago by Dally at St. Thomas's Hospital in London.[1] Although Dally's measures appear somewhat heavy-handed, we ought not over-emphasize our reservations about a treatment as effective as this one for an often intractable condition with death rates as high as 20 percent.

Under the Dally program, a patient is admitted to hospital, put in bed, and told that she must stay there until she has regained a definite, usually quite substantial, amount of weight. Chlorpromazine is administered in liberal, if not positively radical, dosage—as high as 1 or even 1.5 grams a day for patients who may weigh no more than 60 pounds. Tricyclic antidepressant agents may be administered if a patient is depressed. Food is offered in rapidly increasing amounts to totals as high as 4,500 calories a day. Formal psychotherapy is not attempted until a patient's weight is at or near normal level. The program is, at the least, inelegant; but the proof of the pudding is in the eating, and results are surprisingly good. Weight gains averaged over 4 pounds a week in more than 50 patients treated in this manner and four to six weeks in the hospital were usually sufficient to terminate the acute attack.

An esthetically more pleasing approach to treatment of the acute phase of the illness was ushered in nine years ago with a case report on the success of operant reinforcement techniques.[2] Starting from B. F. Skinner's dictum that "behavior is maintained by its consequences," the therapists initially removed from the patient all such pleasant diversions as contact with visitors and other patients, watching television, and so forth. Then they arranged for the reintroduction of these events, contingent upon the patient eating and gaining weight. The result was a surprisingly rapid gain in weight.

The application of operant reinforcement procedures was rapidly developed by groups at the Universities of Mississippi and Pennsylvania,[3-5] now happily united at Stanford. Both groups were able to equal Dally's weight gains of over 4 pounds a week and to do it with limited or no psychopharmacological assistance in a total of 25 patients. In the course of this work, as is noted in the specialty conference, we documented the hyperactivity of many anorexic patients by using mechanical pedometers. And when the opportunity for such hyperactivity—by passes outside the hospital—was made a consequence of weight gain, it proved so strong a reinforcement that, for many patients, none other was needed. A simple inducement—the patient was given a six-hour pass outside of the hospital on any day on which she weighed at least a half pound more than the previous day—was, by itself, sufficient to interrupt the course of this resistant illness in several instances.

Why and how such a simple reward works is still unclear. Agras et al suggest that the most important element is the feedback of information as to caloric intake and the body weight,[3] and they are probably right. Why it should be so effective is still unclear.

To date, behavior modification has been applied almost exclusively in the hospital to patients during the acute, life-threatening, phase of the illness. We have no information as to its success in the longer-term management of anorexic patients.

The third, and newest, therapeutic method to arouse interest has the virtue of being the first to

be of use both in interrupting the acute episode *and* in longer-term management. It is family therapy.

Very little information about the application of family therapy to anorexia nervosa has yet appeared in print. But those who have watched the work of Minuchin and his group at the University of Pennsylvania are impressed that a major therapeutic innovation is at hand. Not only has the acute phase of the illness been interrupted, but favorable long-term changes in the patients have apparently been achieved by modifying the pathological interactions within these "enmeshed" families. A verbatim account of an initial interview with a family with an anorexic daughter, one of the few published accounts of the method, provides an instructive account of the process and leaves us eager for more traditional forms of scientific reporting.[6] (ADDENDUM: Such a report has just appeared. See Reference 7.)

Psychopharmacology, behavior modification and family therapy, even in their current underdeveloped states, have already made it possible to interrupt acute episodes of anorexia nervosa with great predictability. Such a course should be pursued vigorously; there is no longer an excuse for delay in restoring weight to these unhappy patients. And down the road beckons the hope of doing far more than just interrupting acute episodes. We may well be on the threshold of definitive treatment of the disorder.

ALBERT J. STUNKARD, MD
Professor and Chairman
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine

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Refresher Course in Cardiac Radiology

A REFRESHER COURSE in cardiac radiology will be held by the North American Society for Cardiac Radiology from March 2 to 6, 1975, in Williamsburg, Virginia. A distinguished faculty will conduct seminars covering the radiology of acquired and congenital heart disease and its clinical implications.

For further information, please write to:

—KLAUS RANNIGER, MD
Medical College of Virginia
MCV Station, Box 2
Richmond, Virginia 23298

CASE REPORTS

Refer to: Behrstock BB, Petrakis NL: Permanent subcutaneous gold acupuncture needles. West J Med 121:140-142, Aug 1974

Permanent Subcutaneous Gold Acupuncture Needles

BARRY B. BEHRSTOCK, MD
NICHOLAS L. PETRAKIS, MD
San Francisco

ACUPUNCTURE, THE ANCIENT CHINESE ART of inserting thin needles into various points on the body as an anesthetic or for treating various ailments, has recently attracted enormous interest in this country and gained some degree of acceptance by Western medicine. As more people examine this art, the complexity and variety of its techniques and styles are becoming apparent. Because of an incidental radiological finding, an alternative form of acupuncture treatment was brought to our attention: the permanent placement of acupuncture needles. This method, described and practiced by a few acupuncturists in the Far East, has had little or no previous description in the Western literature.

Report of a Case

A 44-year-old Korean woman was admitted to the University of California, San Francisco, Medical Comprehensive Clinic with complaint of right posterior pleuritis-type chest pain of approximately three years' duration. She stated that the pain had become noticeably more severe at the time her late husband was unexpectedly found to have lung cancer, which later caused his death.

Six years ago she had accidentally "rolled down a flight of stairs," causing a back injury and necessitating her admission to hospital for two weeks. She reports having had "no broken bones" and was without noticeable discomfort within three months. One year later the patient began having brief attacks of mid-back pain. As a result, she saw an acupuncturist for five consecutive treatments over a five-month period, reporting symptomatic relief after the first therapy. There was no pain until three years ago, when she began noticing fleeting mid-back and right posterior chest pain, unrelated to exercise and relieved by application of an electric heating pad. When the patient was seen for the first time in the medical clinic with complaint of increased pain, she expressed the fear that she might have cancer. She had no history of smoking or drinking, or of cardiac or pulmonary disease. Results of physical examination were completely normal except for two findings: (1) first percussion tenderness over the 6th to 8th thoracic spinous process and right costovertebral angle, and (2) a coarse, reticulated, hyperpigmented skin change in a radicular pattern in the subscapular and right mid-thoracic region. This coincides with the site of application of the heating pad and was characteristic of erythema ab igne.

X-ray examination of the spinal column and rib detail films showed no evidence of a neoplastic or degenerative process. An x-ray film of the chest showed no abnormalities except for the presence of twenty-two 0.5 to 1 cm metallic densities in the subcutaneous tissue along the entire back and supraclavicular regions bilaterally (see Figure 1). At the time the films were taken the nature of these foreign bodies was unknown to the radiologist. After two months of conservative medical therapy, the patient was without pain.

At first it was our opinion that the linear metallic densities represented accidentally broken tips of acupuncture needles. However, further questioning revealed that the patient was aware of their presence. She said that it is common for Korean acupuncturists to insert gold needles for people with adequate financial resources. She had been told that these needles would stay perma-

From the Division of Ambulatory and Community Medicine, the Department of International Health, and the G. W. Hooper Foundation, University of California, San Francisco.

Submitted November 9, 1973.

Reprint requests to: N. L. Petrakis, MD, University of California, San Francisco, San Francisco, CA 94143.

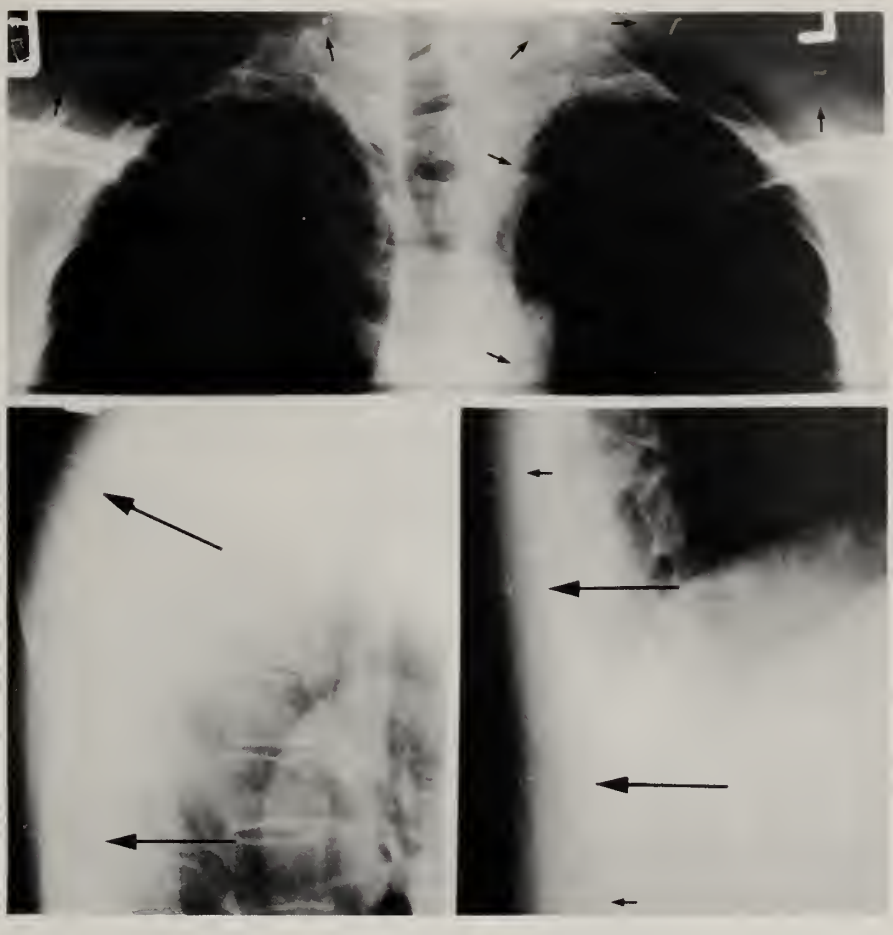

Figure 1.—Arrows indicate locations of acupuncture needles in the subcutaneous tissues above the clavicles and in the back.

nently in place and provide relief for 15 years. Biopsy studies to confirm their true metallic nature were not made.

Discussion

Acupuncture needles may be left in the subcutaneous tissue for either of two reasons. First, they may be left intentionally as a form of "longer therapy," as was done in this case. We found no reference to this practice in the English language literature, but did find one Japanese text that had a section translated to read "On Broken Needles."[1] This source referred to a "new form" of treatment called "the broken or thrown out needle treatment." The author states that the needles are inserted approximately 3 cm into the skin and broken off in place. This is usually done "around the hips where the muscle is thick," and reportedly works as a "stressor." Also, acupuncture needles occasionally are left inserted intact for an extended period. In such instances the needles are usually taped to the skin to prevent them from entering the tissue and moving subcutaneously.

The second and more likely explanation for an isolated acupuncture needle seen in x-ray films or in tissue biopsy studies is that the needle was unintentionally broken off by the therapist, who then was unable to retrieve it. Although only one reference to such accidental breakage can be found in the English language literature,[2] the oriental literature contains multiple references to "broken needles."[1,3] The previously mentioned Japanese text translates ". . . if the broken needle cannot be removed, then even if left in place there will be pain the first two or three days, but no harm. Eventually they have new reactive tissue grow around them in a foreign body reaction and form a lump."[1] A 1955 Chinese acupuncture text explains that "naturally, many broken needles have been left in place since the old days, with no harm reported. They used to be more common when the older, more brittle iron needles were used. If the patient would tense up his muscles the needles would break."[3]

The choice of gold needles for the patient in the present case also raises the question of what determines the material of the needle. Louis Moss[4] states that one can use any metal that produces

needles meeting certain criteria: very fine, flexible, well-polished, and, most of all, not breakable. In the past, non-metallic substances such as bamboo have also been used for needles. Felix Mann, in his recent book on acupuncture,[5] states that silver alloys have the advantage of having some self-sterilizing properties but that for very thin needles they are too soft, and stainless steel must be used. However, Manaka[6] states that some ancient Chinese masters attribute particular qualities to the color of the metal: Yellow (gold) is used for "stimulating or tonifying depleted energy," white (silver) for "depressing excess energy." He also refers to some recent investigations by Western researchers where the impedance at various electric terminal points is affected by the type of metal used to make the needle. Other authors relate the choice of metal to the Chinese principles of Yin and Yang, feminine and masculine forces in nature: Gold, the metal of Yang, should be used for diseases of Yin, and silver for diseases of Yang. But with the general acceptance of the principles of asepsis it was found that stainless steel needles were the most practical because they could be most easily sterilized.[7]

Summary

Subcutaneous linear metallic densities were seen in x-ray films of the back of a 44-year-old Korean woman. Acupuncture needles had been permanently placed in that position six years before as treatment for acute back pain. These gold needles bring to our attention two facts. First, acupuncture needles may be found in subcutaneous tissue either as a result of their intentional placement there or because of accidental breakage. Second, the material of which the needles is made is felt by some therapists to have special significance.

ACKNOWLEDGMENT

We thank Mrs. A. Minami, Oriental Collection Librarian at UCSF, for translating passages from references 1 and 3.

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Tick-Bite in Oregon: Paralysis in California

RICHARD W. EMMONS, MD
Berkeley

F. MICHAEL BREWSTER, MD
Concord

BERNARD C. NELSON, PhD
Berkeley

TICK-BITE PARALYSIS is well-known in the United States and Canada, and case reports are too numerous to permit reference to all. However, despite the abundance of Dermacentor andersoni and Dermacentor variabilis ticks (the most common carriers of the disease) and reports of cases in deer, cattle, horses and other animals associated with Dermacentor occidentalis in California,[1-3] no reports of human cases acquired in California have been published, so far as we are aware. There is only one previous report of a case in California with out-of-state acquisition—that of a three-year-old girl with tick-bite in Oregon, diagnosed in Oakland, California, in June, 1960.[4] We wish to record a second case, that of a three-and-a-half-year-old girl who was bitten by a tick in La Grande, Oregon (a well-known endemic area for tick-bite paralysis), but who became ill in Contra Costa County, California.

The patient is an otherwise healthy child with normal growth and development and no significant antecedent illnesses. On the evening of June 26, 1972, she was noted to have some difficulty getting out of the car just after arriving home from a trip to Oregon. The following morning she had great difficulty in standing, sitting or walking. When seen by one of us (F.M.B.), she was alert, cooperative, and afebrile. Results of physical examination were normal except for weakness and

From the Viral and Rickettsial Disease Laboratory and the Vector Control Section, California State Department of Health, Berkeley.

Submitted February 4, 1974.

Reprint requests to: R. W. Emmons, MD, Public Health Medical Officer, Viral and Rickettsial Disease Laboratory, California State Department of Health, 2151 Berkeley Way, Berkeley, CA 94704.

ataxia. The neck was supple and general muscle tone was normal; there was no nystagmus and cranial nerve function was unimpaired. The deep tendon reflexes were not obtainable. Plantar reflexes were flexor. On sensory examination (light touch and pin prick) no deficiencies were noted. The patient was admitted to hospital for more thorough examination. A partially engorged female D. andersoni tick was then discovered attached in the hair line of the occipital region and was removed. The patient showed rapid improvement thereafter, and it was not felt necessary to perform a spinal tap or other diagnostic tests. She was discharged essentially asymptomatic the following day.

Discussion

Tick-bite paralysis often presents a diagnostic puzzle and may be rapidly fatal if not recognized in time. A tick usually must be attached for four to six days before symptoms appear. Characteristically, there is an ascending symmetrical paralysis without antecedent symptoms; there are no paresthesias or other sensory changes and no fever; the cerebrospinal fluid is normal, the electromyogram shows decreased conduction velocity and decreased muscle action potential amplitude, and an engorging tick is found, often hidden in the hair. Symptoms usually recede rapidly upon removal of the tick, but respiratory paralysis may occur and the toxic effects can be irreversible if too great a delay has occurred. These features together allow differentiation from Guillain-Barre syndrome, Eaton-Lambert disease, myasthenia gravis, poliomyelitis, botulism, diphtheritic polyneuropathy or other causes of paralysis. Several recent reviews or case reports have detailed recent knowledge of the disease.[5-8]

Physicians in California should consider this disease in the differential diagnosis of paralytic illness, and should take a careful history of recent travel and possible tick exposure. The patient should be examined thoroughly for attached ticks, particularly in the scalp. If a tick is found, examination of the entire body should be completed, for there may be other ticks attached. Ticks should be removed by gentle traction with forceps, with care taken not to tear the body from the head. The tick should be kept alive and sent to an expert for species identification. The patient should be observed for a week or two. Acute and convalescent-phase blood specimens should be saved, since further research is needed on tick-bite paralysis and since other diseases such as Colorado tick fever, Rocky Mountain spotted fever and tularemia could subsequently result from the tick bite, and specific serologic tests would be needed for diagnosis.

Summary

A case of tick paralysis in a three-and-a-half-year-old child in California who acquired the tick bite in Oregon is reported. This is only the second such case on record. In California, the disease-producing ticks have been found affecting domestic and wild animals, and could also affect man.

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Localization of a Parathyroid Adenoma by Thermography

EUGENE C. WASSON III, LCDR, MC, USNR
San Diego

JOHN L. SMITH, MD
JAMES A. USSELMAN, MD
La Jolla

PRIMARY HYPERPARATHYROIDISM is being diagnosed at an earlier stage in its course and with greater frequency largely as a consequence of using automated biochemical screening to detect elevated levels of serum calcium. Confirmation by direct quantitation of serum parathyroid hormone has been made possible through the development of a radioimmunoassay for parathyroid hormone by Berson and Yallow,[1] with some modification by Arnaud.[2] A significant proportion of patients with primary hyperparathyroidism are asymptomatic and without complications when the diagnosis is first made, and a question exists as to which of them needs surgical treatment.[3] However, once that decision has been reached, regardless of whether the patient is symptomatic or not, there arises the difficulty of preoperative localization of the abnormal parathyroid tissue.

In 80 to 90 percent of cases of proven primary hyperparathyroidism a single benign adenoma is the cause.[3-5] Approximately 90 percent of the adenomas are located in the neck, with the inferior parathyroid glands affected in nearly 80 percent.[5,6] Yet surgeons are plagued by difficulties in removing an abnormal parathyroid gland and identifying the remaining normal glands. Efforts at preoperative localization have either yielded poor results or been technically difficult and of risk to the patient. A palpable adenoma occurs in fewer than 2 percent of cases, most nodules identified in the anterior neck being of thyroid origin.[7] By contrast, in patients with parathyroid carcinoma, the lesion is palpable in 46 percent.[8] Rarely will a roentgenogram of the neck show a calcified adenoma;[9] extrinsic impression by an adenoma on cine cervical esophagram is reported in fewer than 10 percent.[7]

Scintiscanning with selenomethionine was of value in only 50 to 60 percent of patients studied.[10,11] Retrograde thyroid venography as described by Shimkin and Doppman[12] disclosed only four of ten proven adenomas. Arteriography of the thyrocervical trunk has been used but currently is largely supplanted by selective catheterization of the thyroid venous plexus with radioimmunoassay for parathyroid hormone concentration in obtained samples.[5,7,13-15] Venography has had quite varied results, with Powell[13] noting correct localization in all of 21 patients having single and multiple adenomas while O'Riordan[5] in his series of 29 found the method unpredictable in five and misleading in two others. This he believed was due to low output of parathyroid hormone by the abnormal gland; and he decided finally that the ratio of parathyroid hormone in the blood specimens must be greater than 1 to 7 for diagnosis. O'Riordan also stated that he believed the success rate would be still lower in patients with mediastinal adenomas.

A new method of identifying the site of abnormal tissue responsible for hyperparathyroidism, recently reported by Samuels, Dowdy and Lecky,[16] involves the use of thermography and appears to hold much promise. They report on 18 patients with primary or secondary hyperparathyroidism operated on after thermograms indicated the presence of abnormal tissue. In 17 patients the abnormal tissue was correctly localized, the only false positive interpretation being follicular thyroid carcinoma in a man later found to have a mediastinal parathyroid adenoma. The case presented here was our first opportunity to show, using this diagnostic method, the precise anatomic position of a parathyroid adenoma.

Report of a Case

A 56-year-old Caucasian woman was admitted to hospital for confirmation of a recently made diagnosis of primary hyperparathyroidism. During the preceeding three to four years she had had episodes of anorexia, nausea and epigastric pain. More recently she had noted polydipsia, polyuria and increasing fatigue. No history of bone pain

From the Radiology Division, Scripps Clinic and Research Foundation, La Jolla, California.

Submitted, revised, March 22, 1974.

Reprint requests to: J. A. Usselman, MD, Division of Radiology, Scripps Clinic and Research Foundation, 476 Prospect Street, La Jolla, CA 92037.

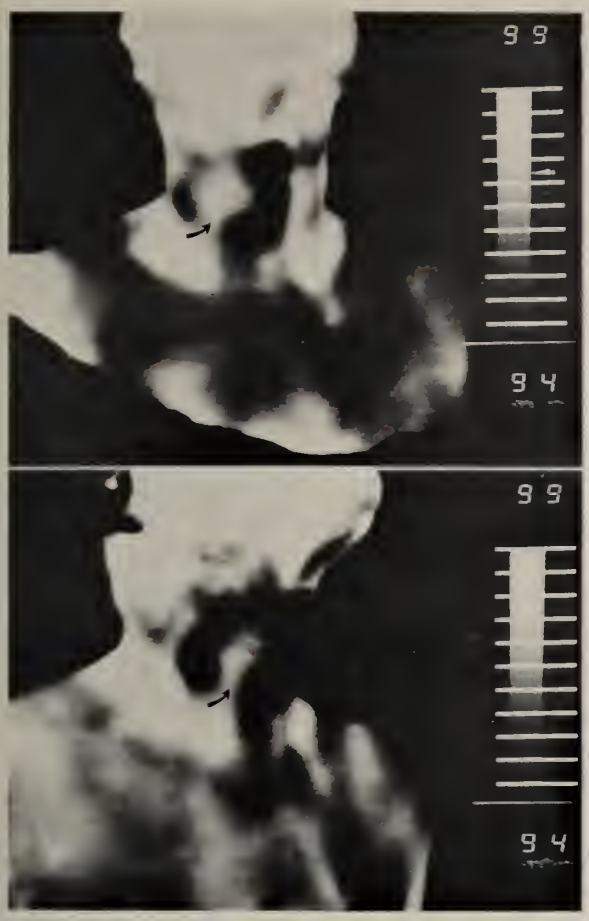

Figure 1.—Anterior and right anterior oblique thermograms of the neck show a focus of increased heat in the right infrathyroid region (arrows). Polarity is adjusted, with white representing increased skin temperature, and black the cooler areas.

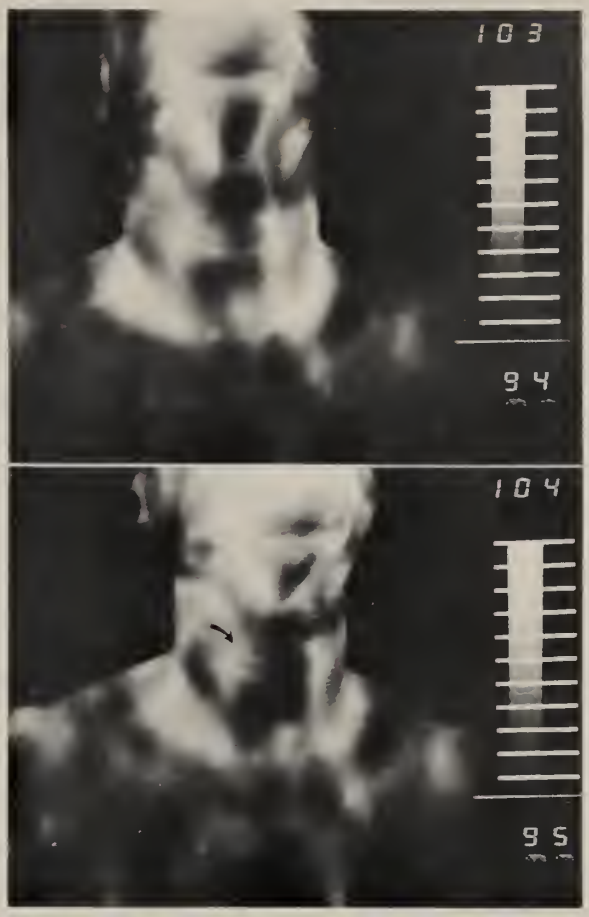

Figure 2.—**Upper frame,** anterior view after surgical operation. There is no localized zone of abnormal temperature as shown in Figures 1A and 1B. **Lower frame,** slight right anterior oblique after surgical operation. Arrow indicates site of operation. There is no longer an area of abnormal temperature.

was elicited. Sudden, severe cramping abdominal pain with radiation to the left flank, and nausea and vomiting, necessitated entrance to another hospital one month before admission here. At that time an intravenous pyelogram showed bilateral calyceal stones and partial obstruction of the distal left ureter by another calculus which passed spontaneously during the examination. It was composed of calcium phosphate. The results of several laboratory tests were abnormal: serum calcium 13.6 mg per 100 ml, with repeat 12.1 mg per 100 ml; serum inorganic phosphorus 2.4 mg per 100 ml; and alkaline phosphatase 120 milliunits per ml. Results of urinalysis showed microscopic hematuria. Serum proteins, uric acid and blood urea nitrogen were within normal limits. Serum parathyroid hormone measured by radioimmunoassay was 450 picograms (pg) per ml (normal mean 255 pg per ml with standard deviation 82 pg per ml), with a simultaneous serum calcium 6.9 mEq per liter.

On consultation at this institution, no significant additional history was obtained. No mass was palpable in the neck. Serum calcium remained elevated, 13.7 mg per 100 ml. Fractionation of a minimally elevated total serum alkaline phosphatase showed normal levels of liver alkaline phosphatase and slightly elevated bone alkaline phosphatase. Radiographs of the hands, chest, abdomen and upper gastrointestinal tract were interpreted as normal. Thermograms (using the Texas Instruments' ThermIscope®) of the anterior neck with contrast enhancement by alcohol-cooling of the skin showed a persistent area of increased temperature (Figure 1) involving the right infrathyroid region. Exploration of the neck was carried out two weeks later, and a 2 by 3 by 3 cm tumor was found lying infralaterally to the

lower pole of the right lobe of the thyroid gland. Histologically, this was a parathyroid chief cell adenoma. The patient's postsurgical course has been uncomplicated and serum calcium levels have returned to normal. Another series of thermograms obtained one month after operation disclosed no evidence of the previously noted abnormal focus of increased temperature (Figure 2).

Discussion

Thermography is the production of a visual image of an object's infrared (heat) emission. This procedure is of benefit in many branches of clinical medicine and research, with other uses still in the investigative phase. A review of the current thermographic literature is not warranted in this report, but instead we emphasize a newly reported application of thermography. The thermograms were made with the patient in a sitting position and the neck comfortably extended, following 10 minutes with neck and upper thorax exposed at 21° C (69.8° F), the temperature maintained in the examination room. Anteroposterior and both anterior oblique views, each requring 4.5 seconds, were obtained before and after application of alcohol to the examined area. This study enabled preoperative localization of a parathyroid adenoma in a patient with primary hyperparathyroidism who had presented with nephroureterolithiasis and hypercalcemia. This is not an unusual case. In a prospective study by Purnell,[3] primary hyperparathyroidism occurred twice as frequently in women and 78 percent of their proved cases were in the 40 to 70 year age group. Another recent study of this disease[17] showed that symptomatic patients had a mean duration of symptoms of 6.5 years before diagnosis. The reported incidence of renal lithiasis ranges from 51 percent[3] to 75 percent.[18]

Although the case here reported brings the number of reported positive thermograms in proven parathyroid disease to only 18, it calls attention to this additional, rapid, simple and noninvasive method of localizing abnormal parathyroid disease preoperatively. The technique is sensitive enough that one gland as small as 3 mm in diameter was accurately localized.[16] Normal thyroid and parathyroid tissues are not visualized, and often it is possible to distinguish between abnormal thyroid and parathyroid disease by radioactive thyroid scan. Thermography of the neck, therefore, is suggested as the first procedure to be used in determining the site of a parathyroid adenoma. Of course, thermography may offer little or no help in a positive sense in detecting parathyroid adenomas lying in the upper mediastinum since the amount of overlying tissue would obscure any temperature gradiant within the lesion and the known variability of the thermal pattern of the anterior chest wall would tend to obscure a small localized zone of increased temperature.[19] These cases then necessitate use of the more complicated invasive procedures.

Summary

Preoperative determination of the site of a parathyroid adenoma often is difficult and fruitless. In the case of primary hyperparathyroidism in a 56-year-old woman here reported, resection of a single parathyroid adenoma was simplified by precise localization of the lesion by thermography. From review of the literature it appears that thermography of the anterior neck may improve surgical treatment of this disease by determination of the anatomic position of the abnormal tissue before surgical operation.

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Tricuspid Atresia and Aortic Origin of Right Pulmonary Artery in a Nine-Year-Old Girl

LAWRENCE L. MENZER, MD
MASATO TAKAHASHI, MD
Los Angeles

ALTHOUGH TRICUSPID ATRESIA and origin of the right pulmonary artery from the aorta (hemitruncus arteriosus) are rare congenital lesions, each has been well described both as an isolated lesion[1-5] and in association with other cardiac defects.[1,2] However, the occurrence of these two lesions together has not been reported. The purpose of this report is to present a case of such a combination of lesions in a nine-year-old girl and to discuss some of the implications of the two lesions on the patient's clinical course.

Report of a Case

The patient, who had weighed 4 pounds at birth, after an uncomplicated 34-week pregnancy, was noted to be cyanotic several days after birth. At two weeks of age, cardiac catheterization was performed elsewhere and tricuspid atresia was diagnosed. The patient was digitalized and for the next five years did fairly well except for five or six admissions to hospital for pneumonia or congestive heart failure or both. Although she had decreased exercise tolerance she remained fairly active. There was no history of squatting or of hypercyanotic episodes.

The patient was first seen at Childrens Hospital of Los Angeles in June of 1972 when she was nine years old. At that time she was observed to be small and thin and in no acute distress. Her height was at the tenth percentile and her weight at the third percentile. Blood pressure was 110/60 mm of mercury, repiratory rate 24 per minute and apical pulse was 80 beats per minute and regular. Mucous membranes showed mild cyanosis. The lungs were clear to auscultation and percussion. On examination of the heart, a generally hyperactive precordium was noted, with a visible and palpable apical impulse at the fifth left intercostal space along the anterior axillary line. The first heart sound was loud and the second sound was single and very loud. There was a grade III/VI harsh systolic ejection murmur which was heard best at the mid-left sternal border with radiation to the base, the apex and, faintly, to the back. There was no diastolic murmur or other abnormal sound. The edge of the liver was felt 2 cm below the right costal margin. Moderate clubbing and cyanosis of the nailbeds were noted. The left radial pulse was diminished but all the other pulses were intact and normal. Results of neurological examination were within normal limits. Hemoglobin was 14 grams per 100 ml of blood and the hematocrit was 44 percent. An electrocardiogram was consistent with left ventricular hypertrophy with left axis deviation (−10 degrees). A chest roentgenogram showed cardiomegaly with prominent main pulmonary artery segment and increased vascularity. There was no difference in the vascular pattern between the right and left lungs.

TABLE 1.—*Catheterization Data*

	RA	*LA*	*LV*	*A_o*	*RPA*
Oxygen saturation	75%	82%	84%	84%	84%
Pressure (mm Hg)	a=14	a=12	100	100	100
	v=11	v=9	10	60	60
	m=11	m=9			

RA = Right Atrium
LA = Left Atrium
LV = Left Ventricle
A_o = Aorta
RPA = Right Pulmonary Artery

Pulmonary to systemic flow ratio approximately 1:1 (assuming pulmonary venous blood saturation as 95%)

On December 21, 1972, right and left heart catheterization was carried out (Table 1). Both right and left atrial pressures were elevated with prominent A and V waves. Left atrial, left ventricular, and aortic oxygen saturations were essentially the same. The catheter was advanced from the right atrium through an atrial septal defect into the left atrium and then into the left ventricle. From this point the catheter was passed antegrade through the aortic valve into the ascending aorta and thence into the right pulmonary artery. Pressure and oxygen saturations in the ascending aorta and the right pulmonary artery

From the Division of Cardiology, Childrens Hospital of Los Angeles and the Department of Pediatrics, University of Southern California School of Medicine, Los Angeles.

Submitted November 15, 1973.

Supported in part by the Childrens Heart Foundation of Southern California.

Reprint requests to: M. Takahashi, MD, Childrens Hospital of Los Angeles, 4650 Sunset Blvd., Los Angeles, CA 90027.

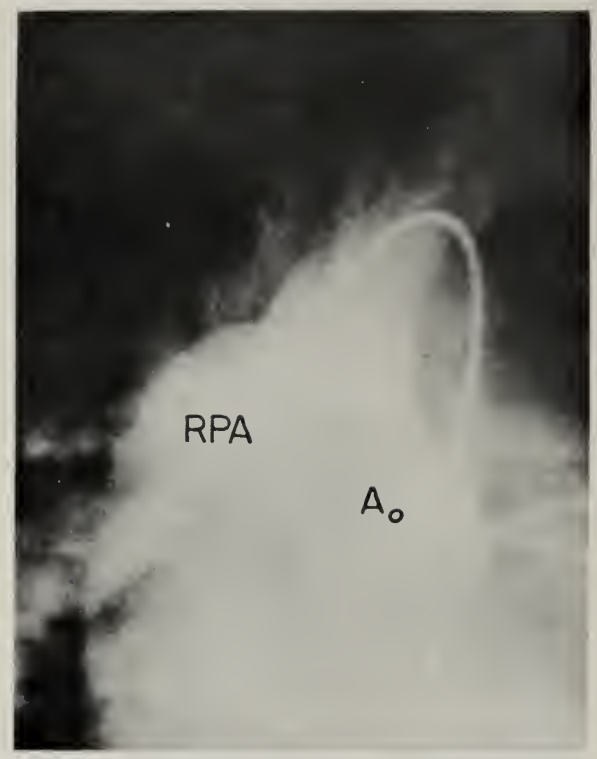

Figure 1.—Right pulmonary artery originating from ascending aorta. (A_o=aorta; RPA=right pulmonary artery).

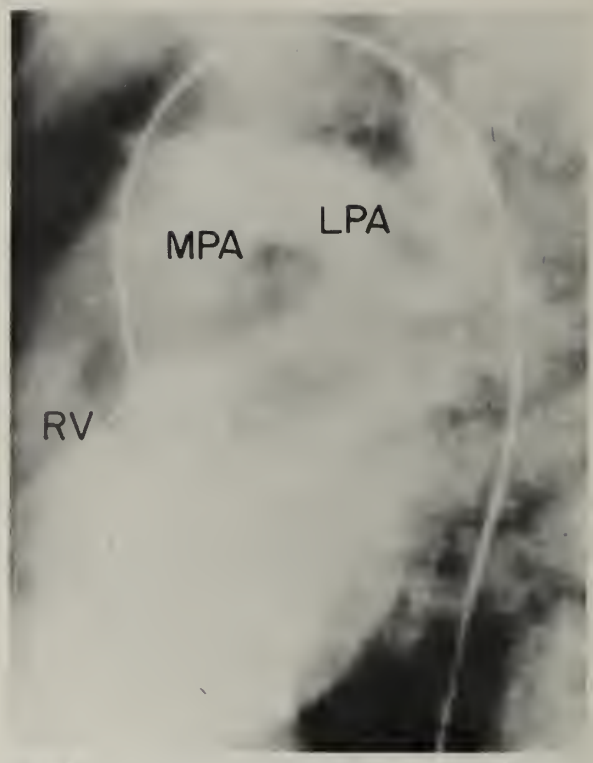

Figure 2.—Hypoplastic right ventricle with main pulmonary artery giving origin only to left pulmonary artery (RV=right ventricle; MPA=main pulmonary artery; LPA=left pulmonary artery).

were identical. Cineangiography confirmed the presence of a large right pulmonary artery originating from the ascending aorta (Figure 1). Contrast medium injected into the left ventricle demonstrated a ventricular septal defect with a hypoplastic right ventricle. The main pulmonary artery originated directly from the right ventricle and gave origin only to a left pulmonary artery, which was normal in size and position (Figure 2). The pulmonary valve appeared normal without any evidence of stenosis. It was not possible to pass the catheter through the ventricular septal defect into the right ventricle and left pulmonary artery.

Discussion

The most remarkable aspect of this case is the patient's ability to function in a relatively normal fashion. Despite her (minimal) decrease in exercise tolerance she remains active and interacts with her peers quite well.

Coexistence of tricuspid atresia and hemitruncus arteriosus in the same patient has not been previously reported to our knowledge. According to Keith and associates,[2] the only aortic anomalies known to be associated with tricuspid atresia are: (1) right aortic arch (8 percent), (2) D-transposition (27 percent), (3) L-transposition (4 percent) and (4) coarctation of the aorta (7 percent). So rarely do these lesions occur together that it is highly unlikely that a single error during embryogenesis could have caused both lesions in the present case.

Tricuspid atresia with hypoplastic right ventricle is thought to occur as a result of unequal division of the primitive ventricular chamber by the developing ventricular septum and endocardial cushions. Aortic origin of the right pulmonary artery on the other hand is said to be due to misplaced attachment of the right sixth aortic arch to the future aortic side as the truncus is divided by the spiral septum. Both developmental errors probably occurred between the 31st and 37th day of embryonic development. One may speculate that a common factor may be responsible for the simultaneous occurrence of these random errors in two separate points in the embryo.

Using the classification of Keith and associates,[2] the anatomy of this child's cardiac lesion approximates tricuspid atresia type 1-C in which an atretic tricuspid valve occurs concomitantly

with normally related great arteries, non-obstructive ventricular septal defect and pulmonic valve and relatively mild hypoplasia of the right ventricle. These features tend to favor increased pulmonary blood flow and this would explain the dilated main pulmonary artery and left pulmonary artery. In addition, progressive development of pulmonary vascular obstruction would cause further dilatation of these vessels. Addition of the aortic origin of the right pulmonary artery (hemitruncus) would certainly contribute to pulmonary over-circulation. Indeed, the patient's history of repeated episodes of congestive heart failure and pneumonia in early life suggests pulmonary over-circulation during those years.

Pulmonary hypertension was noted in the right lung, according to our catheterization data; and from the pulmonary-to-systemic flow ratio of approximately 1:1, it appears probable that pulmonary vascular obstruction exists in both lungs. Whether this process is more severe in the right lung than in the left is speculative. The progressive symptomatic improvement in this patient as she grew is most likely due to the protective effect of the pulmonary vascular obstructive disease. At present the sum of the blood flow to the right lung from the ascending aorta and the flow to the left lung from the right ventricle seems to be nearly ideal, in that she remains free of symptoms attributable to either of the extremes of pulmonary flow. How long this happy situation will last is not known. If the patient's condition begins to deteriorate, as evidenced by increasing cyanosis, it would behoove us to repeat heart catheterization to determine right ventricular and left pulmonary artery pressures and thus determine whether obstruction exists at the right ventricular outflow tract or at the ventricular septal defect. If obstruction were found, then palliative surgical operation might be offered, though if the obstruction were at the pulmonary vascular level no surgical palliation is possible.

At present the child is doing quite well and management consists of frequent clinical evaluation.

Summary

A nine-year-old girl had both tricuspid atresia and aortic origin of the right pulmonary artery. Embryologically these two lesions seem to be the result of separate errors in the division of the truncus arteriosus and the septation of the primitive ventricle. The reason for the progressive improvement in this child's symptoms may be attributable to the pulmonary vascular obstructive disease.

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LETTERS *to the Editor*

Legg-Calvé-Perthes Disease

To the Editor: We would like the opportunity of responding to Dr. G. Wilbur Westin's demurrer in the April, 1974, The Western Journal of Medicine [Westin GW: Legg-Calvé-Perthes (Editorial) West J Med 120:314, Apr 1974] to the ideas about the proof of efficacy of treatment in Legg-Calvé-Perthes disease. Dr. Westin states: "To accept the concept that 'there is no difference in the long term results of the treated or the untreated care of Legg-Perthes' is to condemn a certain number of children to an avoidable hip problem at skeletal maturity." The statement which Dr. Westin places in quotation marks and infers is from the article by one of us (EES) in the same issue, is not quite accurate. What was precisely said was: "No controlled study has ever demonstrated a statistically significant difference between a treated group, regardless of the type of treatment employed, and an untreated group. One recent study indicated no significant difference between treated and untreated groups on a follow-up evaluation after an average of ten and a half years." Dr. Westin's obviously strong feelings to the contrary, the unvarnished facts of the matter are that in spite of a diligent search of the literature, it was impossible to find any statistically validated study which could demonstrate any effective treatment regimen and in fact the study alluded to, in which follow-up evaluations were done at an average of ten and one-half years, was a fairly recent study published in 1971 by a respected British orthopedist.

We would therefore have to ask Dr. Westin to document his statement that acceptance of the concept that there is no difference in long term results of treated or untreated Legg-Perthes, is to condemn a certain number of children to an avoidable hip problem at skeletal maturity. This is not to say that therapeutic nihilism is justified and, as is indicated in the last paragraph of the article, we do, in fact, treat these patients, using the abduction-internal rotation method which has been popularized by Petrie and which does provide containment of the femoral head in the acetabulum. This is done, however, as is pointed out, with the recognition that there is a need for a controlled study with a large enough number of patients to accumulate statistically meaningful conclusions before it can be stated with certitude that treatment is in fact altering the ultimate outcome of the disease process. The problem in evaluating the results of treatment in Legg-Perthes disease, as is pointed out, is that the long term functional prognosis is often surprisingly good in spite of a discouraging roentgenographic picture as well as the initial clinical picture.

Dr. Westin claims avoidance of bilateral occurrence of the disease as an important benefit of the treatment regimen he advocates. Citing Petrie's series of 60 patients and his own study of approximately 20 consecutive patients, he states, "In no patient has the hip that was uninvolved at the time of initial treatment been subsequently involved with Legg-Calvé-Perthes disease." To support the above claim, rates of bilaterality must be shown to be significantly different in groups of treated and untreated patients. This has not been done.

Both Dr. Westin and Dr. Petrie have compared results of treatment in patients presenting with unilateral disease with the rate of bilaterality in the entire population with the disease, excluding from their computations those having bilateral disease at the start of treatment. One cannot tell from Dr. Westin's short article what the rate of bilaterality was in the entire group of patients he studied. Using the data in Petrie's article, it can be calculated that 11.6 percent of his patients presented with bilateral disease. This figure is not significantly different from any previously reported rate for bilaterality in those having the disease. The presence of bilateral disease in patients before treatment, at a rate similar to the entire disease population rate, raises the possibility that the disease most often develops initially as either bilateral or unilateral, and that treatment has little or no bearing on subsequent involvement of the unaffected hip.

This hypothesis could be questioned if it were shown that patients with bilateral involvement were taking significantly longer than patients with unilateral disease to begin treatment, thus allowing time for involvement of the opposite hip. From Petrie's data we calculated the mean interval from time of onset to time of treatment. Contrary to what would be expected if delay were allowing

the disease to become bilateral, we found that patients with bilateral involvement were taking far less time to get to treatment than unilateral patients, in fact less than half the time. While the time between onset and initiation of treatment for bilateral cases was 0.344 years, the comparable figure for unilateral cases was 0.737 years. These figures throw doubt on the efficacy of treatment in prevention of bilaterality and support the idea that bilateral cases are most commonly bilateral from early in the history of the disease.

Finally we should like to say that we do agree with Dr. Westin, whose contributions in this field are well known, that these children should be treated, and in fact should be treated just as he does based upon the best available current knowledge. In particular, we trust that no one will confuse this admittedly stringent interpretation of the literature with inadequate diagnostic measures (inasmuch as other conditions may simulate Legg-Perthes disease but demand different treatment), and similarly with the need for careful follow-up regardless of the treatment elected.

Asking for statistical validation of conclusions regarding treatment methods is not the same as recommending that nothing be done.

ELMER E. SPECHT, MD
HOWARD BARKAN, MPH
San Francisco

Pressure on the Colon

TO THE EDITOR: Doctor Shulman [Shulman AG: High bulk diet for diverticular disease of the colon. West J Med 120:278-281, Mar 1974] deserves credit for calling our attention to new concepts in the field of diverticular bowel disease.

Its increase during the last century he traces to changes in food habits causing a reduction in colonic bulk. Higher intracolonic pressure leads to excessive thickening of the colonic musculature and, in turn, to diverticulosis.

His arguments have a formidable range, from his own clinical observations to experimental work of others, from geographical, historical and statistical data to anthropological evidence.

Yet, besides the mere eating habits, there are, I submit, other anthropological factors which involve the development of diverticular disease:

Cultural: In our lives it is common that people find it either physically impossible or socially improper and embarrassing to promptly answer the call of nature and tend to wait for hours to retire to the stool. When harnessed to our work or engaged in social functions we allow our high intracolonic pressure level to persist and to build up.

In contrast, so I am told from first-hand observation, villagers in India use the open field; women in groups trek out before sunrise for their quick, simple open-air ritual.

Sanitary: Western civilization has tended to give up the outhouse: the place was cold, smelly and verminous. In its unattractive air the task was performed with physiological expeditiousness. In its stead, we now retreat to the comforting privacy of a well-appointed bathroom and, contemplating the decor and sweet scent, we inadvertently delay the healthy release of the intracolonic pressure.

Literary: We literate people have succumbed to a further hazard: I am amazed how many take a magazine or a book with them and read instead of going on with the business at hand. An obnoxious innovation of our civilization is the magazine rack near the stool. It always has suggested to me that diverticulosis coli is in the house. Another added attraction and distraction to prolong the session is a handy radio.

I believe it is fair to postulate that there is, besides the colonic pressure rise per se, the role of a second factor, the *duration* of the high pressure level.

Doctor Shulman's approach should not only reduce the *level* of pressure, by more bulk, but also reduce its excessive *duration* by sounder cultural habits.

E. FRITZ SCHMERL, MD
San Leandro, California

More on Bran

TO THE EDITOR: A correction on the Letter to the Editor by Lucas W. Empey, MD. [West J Med 120:501, Jun 1974]:

Having read and listened to "Mr." Painter of England carefully explain the importance of bran in the diet and *how to use it,* may I detail proper use to avoid chronic pain from excess use.

First, it is the fiber in unrefined bran that is the important ingredient—so whole bran or "natural" bran flakes is to be used, not 40% Bran Flakes® nor compressed pellets such as All-Bran®.

Dosage starts at two teaspoons per day raising it by one teaspoon at weekly intervals until soft easy bowel movement(s) daily ensue. ["9" per day was the highest dose needed, "Mr." Painter stated.]

S. BERKOWITZ, MD
Burlingame

Sublingual Testing in the Diagnosis of Food Allergy

To the Editor: The accurate diagnosis of food allergy has always been difficult, even though there is little problem in identifying a pronounced acute allergic or anaphylactic response to a specific food. The patient and his family usually recognize severe allergy before the physician is consulted in such cases, and the food is avoided. Difficulties arise when symptoms are mild or chronic or when they appear several hours or more following food ingestion. In recent years a number of physicians have used sublingual drop or extract injection techniques to assist in sorting out the less obvious cases of food allergy. Not until recently has either of these techniques been subjected to objective double-blind evaluation. Unfortunately, to date both have been found to be wanting since results were not reproducible when tests were repeated in a different order at a later date.

The writer participated in a study of sublingual tests conducted by the Food Allergy Committee of the American College of Allergists, and thereafter made additional tests by double-blind protocol. The results obtained on the 12 allergic patients studied supported the committee findings, that is, the tests had no reliable reproducibility under double-blind conditions. Several observations of interest were made. Eleven of the 12 reported symptoms following one or both challenges with one or more of the five food extracts or the placebo. Six patients had symptoms following both challenges with an extract, but when the code was broken it was found that symptoms were different after the second challenge in five of the six. The patient whose symptoms were reproduced had similar symptoms following the placebo. Eight of 12 patients reported symptoms following challenge with placebo, four on both occasions. The four had different symptoms following each placebo challenge. Many symptoms previously experienced by a patient reappeared following administration of a food extract or the placebo, but seldom did the symptoms correlate with foods suspected by history.

It is hard to escape the impression left by the over-all study that patient anticipation at times may be a dominant factor in inducing either symptoms or observable responses including rhinorrhea, lacrimation, hoarseness, pruritus, wheezing and changes in the pulse rate.

Indeed, one is led to the speculation that the "apparent value" of such tests as reported by a few physicians experienced in their use may result from the test situation providing an attractive means for the patient to express his conscious or subconscious belief that the food being tested caused untoward reactions in the past. It may be unwise to make a blanket denial that this kind of information could help in the management of selected patients. Nevertheless, since physicians are obliged to provide maximal value for the fees the patients pay, this procedure must be considered experimental at present.

Douglas C. Heiner, MD
Los Angeles

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Disc Lesion Management

To the Editor: In regard to the article on disc lesion management [Blau L, Kent L: Conservative and Surgical Aspects of Disc Lesion Management—Follow-Up Review of 2,214 Cases. West J Med 120:353-357, May 1974] the authors quote their poor results in correlating electromyographic findings with objective nerve root compression. In their discussion of the EMG, they quote from Dr. E. W. Johnson's article, indicating it was used for the format of their electromyographical studies. However, when they describe their procedure, they discuss the resting state which is step one; the minimal contraction which is step three; and the maximum contraction which is step four; but they omitted the insertional activity which is step two in Dr. Johnson's paper.

In reviewing several articles which have been written by Dr. Johnson, he indicates that the most sensitive part of the examination for finding abnormal muscular irritability "positive sharp waves and fibrillation occurs during step two, the insertional activity." If step two of the electromyographical examination was omitted, this could easily account for your rather disappointing results in correlating positive findings of EMG with objective root compression.

J. H. Kennedy, MD
Associate Medical Director
Physical Medicine and Rehabilitation
Rehabilitation Institute of Oregon
Portland

Trauma Rounds

Chief Discussant
DONALD D. TRUNKEY, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Trunkey DD: Assessment and resuscitation of the injured patient (Trauma Rounds). West J Med 121:153-157, Aug 1974

Assessment and Resuscitation of the Injured Patient

DAVID GOHEEN, MD:* The patient is a 19-year-old male student who was injured in an automobile accident. He was not wearing a seat belt and in a frontal collision the steering wheel of the car struck him forcibly in the epigastrium. Initial evaluation showed blood pressure of 60/40 mm of mercury which rose promptly to 120/78 after intravenous administration of one liter of fluid shortly after admission to hospital. His primary complaint was pain in the right side of the chest on inspiration and pain in the upper abdomen. There were no signs of neurological injury and he appeared alert and oriented. On physical examination, lacerations of the neck and chin, and abrasions of both knees were noted. The chest wall was tender, the abdomen was scaphoid with slight tenderness on deep palpation. The hematocrit on admission was 43 percent. The urine was clear.

Thirty minutes later, the blood pressure fell to 90/60 mm of mercury. The facial lacerations were sutured to control bleeding. While x-ray studies were being made, and despite additional fluid administration, the blood pressure fell to 80/40 mm of mercury and signs of peripheral vasoconstriction were noted. After further resuscitation with 2.5 liters of crystalloid solution, the blood pressure rose to 90/60 mm of mercury and the hematocrit was 34 percent. Leukocytes numbered 21,000 per cu mm.

At laparotomy, the peritoneal cavity was found to contain 2 liters of blood and there was laceration across the entire left lobe of the liver. There was massive hemorrhage from the superior portion of the laceration adjacent to the vena cava. Because of disruption of the left hepatic vein a total left lobectomy was necessary to expose the site of injury and control bleeding. Fourteen units of blood were given during the operation. There was no other intra-abdominal trauma. Postoperatively the patient did well except for a minor wound separation.

DONALD D. TRUNKEY, MD:† *Dr. Goheen, how much time elapsed between this patient's hospital admission and definitive surgical operation?*

DR. GOHEEN: Four hours.

DR. TRUNKEY: *Dr. Knudson, you were the chief resident in charge in this case. Do you think this delay was reasonable, considering the grave nature of the patient's injuries?*

JOHN KNUDSON, MD:‡ We were misled in this case and we did underestimate the abdominal injury. The patient originally appeared to respond well

*Trauma Service Intern.

Sponsored in part by NIH grant GM 18470 and the Northern California Trauma Committee, American College of Surgeons.

Reprint requests to: D.D. Trunkey, MD, University of California Service, San Francisco General Hospital, San Francisco, CA 94110.

†Chief of Surgery, Mission Emergency Hospital and Assistant Professor of Surgery, University of California, San Francisco.

‡Chief Resident, Trauma Service.

to fluid resuscitation and examination of the abdomen should no abnormalities. The neck lacerations, which were deep and still bleeding, appeared to account for the blood loss and this is the reason we elected to suture these first. Obviously, in retrospect, we lost ground during the two to three hours the patient was observed. Also, because of the apparently superficial nature of this patient's injury, we had only one catheter in place and when the first fall in blood pressure occurred, it was difficult to administer fluids as rapidly as we would have liked. We lost valuable time attempting to suture lacerations before we carried out a second cutdown in the patient's ankle. Once it was recognized that the bleeding from the laceration was not the only cause of blood loss, the decision to open the patient's abdomen was an easy one, even though the physical findings were negligible.

Dr. Trunkey: This case demonstrates some of the pitfalls we may encounter in the emergency room while resuscitating trauma victims. I would like to spend just a few minutes discussing how best to manage patients of this type and what we can do specifically to avoid these pitfalls.

As soon as the critically injured patient arrives, essential steps must be carried out simultaneously. One is assessing the injury and the second is starting resuscitation. Often these are done at the same time. In order to assess the injury adequately you must quickly remove all the patient's clothing and examine him from head to toe, noting respiration and skin temperature. It is important to roll the patient over and examine his back side. Too often we may completely miss the posterior wounds which actually are the lethal injury. Concomitant with this initial assessment, someone should attempt to obtain a history from either the ambulance attendants or from witnesses of the accident to determine when and how the patient was injured, how much blood was shed at the scene, and how long the delay was between injury and transportation.

The two major priorities are ensuring adequacy of the airway and restoring circulation, in that order. The physician should ascertain (with his fingers, if necessary) that there are no dentures or foreign bodies in the upper airway. Adequate suction and lighting should be at hand. Insertion of an oropharyngeal airway may be necessary to keep the tongue of a comatose patient from falling backward and obstructing the pharynx. Oxygen can be administered by mask and good ventilation obtained without the aid of endotracheal tubes and special mechanical devices. Room air, administered through an Ambu type mask and bag, is adequate for the initial few minutes. Endotracheal intubation can be done after things have settled down, but may be imperative if secretions cannot be cleared from the upper airway because of maxillo-facial injury or aspiration of fluid. Emergency tracheostomy is rarely necessary.

Having assured the passage of oxygen from the environment into the lungs, we now have to assure that it is transported from the lungs to the brain. This requires an adequate circulation and is dependent on the pump and the amount of circulating volume. If there is no pulse when the patient is admitted to the emergency room, closed chest cardiac massage should be started as soon as the airway is established. Large bore catheters should be inserted through cutdowns in upper and lower extremity veins. It is then necessary to differentiate between primary pump failure and defective circulating volume. This is done by examining the neck veins. If the neck veins are distended, resuscitation should be directed primarily toward the heart; if they are collapsed, initial therapy should consist of volume resuscitation.

The cardiac problem that can be corrected most quickly is pericardial tamponade. Tamponade should be suspected in any patient who arrives in the emergency room in shock, has elevated central venous pressure or distended neck veins, and has a penetrating wound which may have hit the myocardium. Tamponade may also be suspected in patients who have had blunt trauma to the anterior chest. If tamponade is suspected, pericardiocentesis should be carried out immediately. An 18-gauge spinal needle should be inserted from the paraxiphoid area obliquely upward toward the left shoulder at an angle of 45 degrees with the skin. The aspiration of as little as 25 to 50 ml of blood may be all that is necessary to provide dramatic relief. A left anterior thoracotomy through the fourth intercostal space, with opening of the pericardium and evacuation of the clot, should be done if the patient does not respond to aspiration or is in extremis, or if tamponade promptly recurs. Any bleeding from the heart can be controlled by sticking a finger into the hole to prevent further blood loss until the patient can be more adequately resuscitated and taken to the operating room for definitive repair. Using such techniques, we are now able to save at

TABLE 1.—*Characteristics of Various Levels of Shock*

Levels of Shock	*Blood Volume Deficit*	*Effect*	*Signs*
Mild	0-20 percent	Peripheral vasoconstriction	Cold, pale
Moderate	20-40 percent	Decreased visceral organ perfusion	Oliguria, anuria
Severe	40 percent+	Decreased heart and brain perfusion	Restless, agitation, stupor, coma

least 50 percent of all patients with penetrating wounds of the heart, provided the patient shows some sign of life when first seen.

Other myocardial injuries that may lend themselves to surgical therapy include myocardial contusion and myocardial infarction. Myocardial contusion may cause bleeding from epicardial vessels and present as tamponade. Contusion may result in impaired pump function and therapy proceeds as it would with primary myocardial infarction.

The second component of restoration of circulation involves assessing vascular volume. We divide shock into mild, moderate and severe, based primarily on clinical criteria (see Table 1). We rely very little on pulse and blood pressure, for these two signs may change only very late in shock, particularly in healthy young adults.

Mild shock is present when approximately 10 to 20 percent of the blood volume has been lost, and it is manifested by poor perfusion of the skin. The patient appears pale. The skin is cool to the touch, starting first in the extremities and progressively involving the trunk. As shock becomes more profound, there is activation of the sympathetic nervous system, with sweating superimposed. The patient usually complains of feeling cold and is often thirsty. Tachycardia may or may not be present.

Moderate shock occurs when 20 to 40 percent of the blood volume has been lost. Physiologic mechanisms come into play to preserve the remaining blood flow to the heart and brain at the expense of all other viscera. The key to monitoring of this stage of shock is the urinary output. For this reason all patients who show signs of mild shock are catheterized and urinary output is carefully monitored. If urinary output is below 0.5 ml per kg of body weight per hour, we can assume that there is pronounced hypovolemia and poor renal blood flow, and that at least 20 percent of the blood volume is depleted.

Severe shock occurs when more than 40 percent of the blood volume has been lost. By clinical definition, severe shock means inadequate perfusion of the two most critical organs, the heart and brain. The cardinal cerebral symptoms are restlessness and agitation, progressive deterioration into stupor and coma, and finally death. Cardiac manifestations at this time may include arrhythmias and evidence of myocardial ischemia on the electrocardiogram. This classification of shock has to be modified for older patients who may have an arteriosclerotic vascular system with a fixed peripheral vascular resistance or a low cardiac index and cannot bring protective hemostatic mechanisms into play. In these patients as little as 10 to 20 percent blood volume loss may cause symptoms of moderate or severe shock.

With these criteria, assessment of the volume status should take but a few seconds and treatment should be begun immediately. This consists of the placement of large bore catheters in venous cutdowns. At this institution we prefer either infant feeding tubes approximately 3 mm in diameter or intravenous extension tubing 5 mm in diameter. The actual cutdown sites may vary depending on the clinical situation; however, the preferred anatomical sites are the basilic vein at the antecubital fossa and the long saphenous vein at the ankle. Both of these are large veins located in a relatively constant anatomical area. The number of cutdowns varies from one to three, depending on the severity of the shock. I feel strongly that in urgent emergency situations percutaneous subclavian or internal jugular catheterizations have no role. Such catheters may produce additional complications and are unreliable in the patient whose blood volume is depleted. The veins in these patients will be collapsed, insertion will be more difficult and complications such as pneumothorax may compound the problems. Subclavian catheterization should be reserved for patients who have pure cardiac emergencies and full vessels or for patients in whom elective placement of the central line is indicated. One of the cutdowns should be in a thoracic location to enable monitoring of central venous pressure. Central venous pressure, in itself, however, is not a reliable gauge of the severity of shock but does tell whether the venous system is empty or full,

whether attention should be directed primarily toward volume or cardiac malfunction, and whether resuscitation is moving in the right direction.

As restoration of the airway and effective circulation are going on, other life-threatening problems should be assessed and treated. The most important is hemorrhage. If blood loss is external, it is rarely necessary to use a tourniquet for control. Direct pressure is almost always successful. Severe, ongoing internal hemorrhage is recognized by progressive deterioration of vital signs. If the circulatory status of the patient is critical and does not respond to 2 liters of crystalloids introduced rapidly for 5 to 10 minutes or if there is a temporary response followed by a fall to the previous baseline in 10 to 15 minutes, internal hemorrhage is severe and prompt and definitive surgical treatment is required. An x-ray film of the chest is helpful if it can be obtained en route to the operating room. If the x-ray film shows the chest to be normal, the problem lies in the abdomen. If arrest from hypovolemic shock occurs, a left thoracotomy and cardiac massage should be done. It is impossible to resuscitate an empty heart with closed chest massage. Maximal use of what volume is left can be achieved by clamping the supradiaphragmatic aorta. The number of these patients saved will not be high.

Tension pneumothorax must be recognized if the patient is to survive. Patients with this condition usually have air hunger or respiratory distress and the trachea is deviated to the opposite side. Other findings include distension of neck veins (as is found in cardiac tamponade), decreased breath sounds on the side of the lesion and tympany on percussion. I would not wait for an x-ray film of the chest to confirm tension pneumothorax but would immediately insert a chest tube into the suspect hemithorax. I prefer to insert all chest tubes in the mid-axillary line in the fifth, sixth or seventh intercostal space. The reason for this is that the patient often has a hemothorax in addition to pneumothorax and drainage of both can be accomplished most adequately if the tube is in this location.

Once these immediate problems are treated and the condition of the patient has stabilized, or if the patient has arrived in a semi-stabilized condition, then one may use the extra time to carry out further clinical assessment. This would include approprate x-ray films to see if there is sequestered blood loss in the pleural space, abdomen or in pelvic or long bone fractures. In addition, one may elect to do paracentesis or peritoneal lavage to evaluate abdominal pain or distension, particularly in a multiply injured or comatose patient. Then the central nervous system should be examined. The initial assessment should include a quick neurologic examination including respiration, level of consciousness, gross motor and sensory function, reflexes and eye signs. If the patient is comatose, his neck should be protected and his head kept in an axial orientation when he is being moved. Cervical x-rays should be taken as soon as practical to rule out cervical fracture. If level of consciousness decreases or lateralizing signs develop during observation, increased intracranial pressure may be assumed. Craniotomy may be necessary. Next, a progressive survey of other systems is conducted. A careful abdominal evaluation is indicated. If the patient has hematuria, special diagnostic studies such as intravenous pyelogram and cystograms are indicated to rule out rupture of the kidneys or bladder. Arteriograms may be obtained for wounds near vessels, particularly those in the mediastinum, the thoracic inlet, the base of the skull and the extremities.

Finally, I would urge that when a patient comes into the emergency room and is conscious, you should explain to him what you are doing. During the resuscitation he will be very anxious because he thinks he is dying. In addition, he will often be in pain and the resuscitative effort may also cause some discomfort. It is a good thing to offer him comfort and reassurance in order to reduce apprehension and the anxiety that may cause neurogenic shock.

Now, in reference to the case presented today, I would like to ask two questions. Doctor Goheen, what was the status of skin perfusion when the patient was first seen—was he warm or cold to the touch? Second, was urinary output monitored during the four hours he was in the emergency room?

Dr. Goheen: The patient was definitely cool and vasoconstricted. Our problem was that we assumed that the superficial lacerations accounted for the blood loss. For this reason, we were reluctant to place a catheter and risk urinary complications in this young, apparently healthy man.

Dr. Trunkey: This reluctance to catheterize the patient is understandable but it obviously resulted in greater hazard to this particular patient.

The inability to properly monitor this patient, who was felt to be in mild shock because bleeding was thought to be under control, resulted in delayed recognition of the abdominal injury. While a four-hour delay before operation did not compromise this patient, we might have prevented a considerable amount of blood transfusion had we elected to carry out laparotomy within an hour of admission. As a matter of fact, all the essentials related to immediate assessment and resuscitation can be carried out within 10 minutes if our team is functioning optimally.

A PHYSICIAN: *What blood tests do you make on your trauma victims?*

DR. TRUNKEY: That is a good question. As soon as a cutdown has been established, approximately 30 ml of blood is obtained. Part of this is immediately sent to the blood bank for type and crossmatch of whole blood. Part is spun down and a hematocrit reading is obtained, although we must remember in acute volume loss that the hematocrit may be normal and misleading. The remaining blood can be spun down and kept for laboratory determinations of such things as serum electrolytes, glucose, blood urea nitrogen and creatinine, or even for toxicology. I would not advocate doing all of these routinely but only as history or further assessment indicates.

A PHYSICIAN: *What fluids do you give the patient after the cutdowns have been established?*

DR. TRUNKEY: I favor initial resuscitation with balanced salt solution and at this hospital we use Ringer's lactate. The amount the patient requires depends on the severity of the injury and the degree of shock, and we give that amount of fluid necessary to restore circulation based on our clinical assessment, evaluation of urine output and the central venous pressure. If the patient does not respond as I indicated previously, then type-specific blood without cross-matching can be added. As a general rule, blood should not be used until the patient is in the operating room and induction of anesthesia is ready to start. This ensures that vital reserves of blood are not simply poured into a body cavity but will be available when they will do the most good. I would not use albumin or its substitutes in acute shock because this material crosses the endothelial membrane and ends up in the interstitial space where it may compound problems by producing a sustained obligatory edema and interfere with organ function. This may be very important in the lung, as it sets the stage for respiratory distress syndrome. Crystalloids (saline solutions) are more easily mobilized and are usually eliminated by the second or third post-injury day. I think albumin and plasma should be reserved for patients with chronic or subacute low blood volume and when there are no signs of moderate or severe shock. The use of dextran as part of initial resuscitation is controversial. Clinical dextran coats the red cell and interferes with blood typing and crossmatch. Low molecular weight dextran may interfere with platelet function and, for those two reasons, I personally do not favor the use of dextrans in the immediate resuscitation. Low molecular weight dextran may be very helpful, though, in specific instances such as when one desires to keep the microcirculation open in crush injuries or in burned patients.

Refer to: Weinberger CW: The guideposts in the RMP odyssey (Government and Medicine). West J Med 121:158-160, Aug 1974

The Guideposts in the RMP Odyssey

CASPAR W. WEINBERGER
Secretary of Health, Education, and Welfare

THE CHRONOLOGY of the Regional Medical Programs extends through one of the most turbulent decades in the history of American health care.

From 1964—when the Report of the President's Commission on Heart Disease, Cancer and Stroke recommended the development of regional complexes of medical facilities and resources—until today, no fewer than 38 laws directly affecting the nation's health care system, not including appropriations legislation, have been enacted. Federal expenditures for the nation's health have risen from about $4 billion in fiscal 1965 to $24.6 billion for fiscal 1972, with $26.3 billion requested by the President for existing health programs in fiscal 1975.

The programs which have been conducted under this legislation, supported by billions of tax dollars, have contributed substantially to improvements in the national availability of health facilities and health manpower and in expanded access to these resources.

The number of active physicians in this country has increased from 280,461 in 1964 to more than 345,000 this year. The number of American medical schools has increased from 87 in 1964 to 114 today. The 1964 problem of scarce hospital beds has now become a problem of how to control the proliferation of unneeded beds and unnecessary duplicative facilities. If we are still confronted by problems in the distribution of health resources, we are at least on the verge of providing the individual citizen with the means for paying for those resources within his proximity. We can expect this period of accelerated progress in the delivery of health care to be capped by the enactment of some type of national health insurance.

If this has been a period of accomplishment, it has also been one of experimentation and learning. We have learned that producing more health manpower and facilities is not necessarily accompanied by improved geographic distribution of those resources. We have learned that improving the quality of health care says nothing about extending that improved care to those who are physically or financially remote from our centers of medical excellence. And we have learned that the price of an improved health care system is not cheap. Last year, expenditures for health care amounted to 7.7 percent of the nation's gross national product, compared with 5.2 percent in 1960.

The proliferation of approaches to American health problems attempted during the past decade has also shown us that a national policy of simply inaugurating a stream of new programs, each addressing only a part of the total health care delivery problem, simply adds to the already great federal health bill and postpones or hampers the task of marshalling federal resources into a comprehensive, coordinated effort.

The fact that these lessons were learned over a period of time, and not as of some precise date, eliminates such factors from any neat chronicle of the fortunes of some individual program—whether it be Regional Medical Programs, Hill-Burton, or health manpower—but the impact is there nevertheless. Further, especially in view of the proliferation of federal programs in the 1960's, a chronicle of the twists and turns of one program

EDITOR'S NOTE: Secretary Weinberger was invited to respond to the commentary "The Curious Odyssey of Regional Medical Programs" which appeared previously in the May issue of this journal. In his response the Secretary places the RMP odyssey in broader perspective and also gives us a glimpse of the future as he sees it. —MSMW

Reprint requests to: C. W. Weinberger, The Secretary of Health, Education, and Welfare, Washington, DC 20201.

should take into account the total context of federal activity within which those fortunes occurred, whether it included increased competition for federal funds, the development of opportunities for administrative improvements, the availability of alternative programs to carry on the work, the implementation of changed views of what constitutes federal responsibility, and the assigning of higher priorities to problems previously submerged.

Even when these considerations are admitted into the discussion of the history of a particular program, there is room for honest disagreement, variations in interpretation, and shades of opinion. The judicial system is as legitimate an avenue to resolving those important differences as direct approaches to the legislative or the executive branches.

Failure to acknowledge that both problems and policies can change and that not everyone will agree with the revised position is to present a distorted picture of seeming inconsistencies, contradictions, and imagined vendettas.

The initial concept of Regional Medical Programs was to provide a vehicle by which scientific knowledge could be more readily transferred to the providers of health services, and by so doing, improve the quality of care provided, with emphasis on heart disease, cancer, stroke, and related diseases. That this original purpose has been broadened or revised or that some categories have been rescinded was inevitable in light of an improved perception of the nature of the nation's health care delivery problem over the past decade. That the utility of the RMP approach in coping with present problems and priorities has been short of the mark, is neither surprising nor a reflection on the integrity or competence of the individual RMPs. Despite the value of the relationships established by the RMPs over the past several years, the RMPs in their present form were simply never envisioned as a vehicle for addressing the comprehensive scope of health care delivery problems in the manner which we believe will be effective and is required today.

From the outset, the RMP has had great difficulty in defining a clear role for itself in concentrating its efforts and resources on even a few, well-selected target areas. At the same time, it has been unsuccessful in reconciling the conflicting and changing emphasis between categorical disease activities and comprehensive health care problems. More than half a billion dollars has been expended via the RMPs in an effort which has neither been true to the program's initial objectives nor sufficiently flexible to fulfill a more comprehensive mission. As a result of court action, another $218 million is being directed into this dubious direction.

Even with the original strong emphasis of RMP on regionalization there is little evidence—and only with regard to kidney disease—that the RMPs have in many areas produced the regionalized systems of health care originally envisioned at the program's outset.

There is no significant evidence that the RMPs have achieved their goal of getting research advances into regular large-scale practice. The training programs undertaken are typically of limited scope and duration, and there is no substantiating evidence that these have had a significant impact on actual medical practice or in demonstrating improved quality care.

A major problem with respect to RMP has been the high cost of maintaining the program, or core, staffs in each of the 56 regions. A significant part of the overall RMP effort and funds has gone to pay for program staff and their activities, including administration, consultation, project development and management, and evaluation.

Another continuing problem has been the relationship of RMPs to Comprehensive Health Planning. In some areas, RMPs and CHPs have worked closely together in a beneficial way, but often their individual roles have been hard to differentiate. It is difficult to have a CHP agency with responsibility for the health planning for an area while another federally-supported program, an RMP, is implementing activities in that same area based on its own planning and priorities. What has frequently happened is that, since the RMP has had funds available to carry out operational activties, its planning has become the deciding force of what is done in a given area. This has not always been consistent with broader community and consumer health needs and interests.

The opportunity for such conflict may be seen from the fact that of the 56 RMP regions, 34 are exactly coterminous with state boundaries and served by CHP agencies.

A solution to this problem has been advanced by the Administration in the form of the proposed

Health Resources Planning Act (S. 3166), which would replace the present RMP and CHP authorities, which expired June 30. The bill has two major purposes: First, to assist the nation's health care system to plan more effectively to provide the resources necessary to meet the nation's health care needs; and second, to grant assistance to states to pay part of their costs in regulating proposed capital expenditures and rate increases for health care.

This proposal provides for a clear distinction between planning and development activities on the one hand and regulatory functions on the other. We believe that the planning function should rest at the local level. It is at this level at which local problems are best understood and can best be solved. On the other hand, we feel that regulatory functions should be placed at the state level, recognizing that regulation is more clearly a government function. We plan, however, that the state regulatory bodies will rely heavily on the local planning bodies for advice in carrying out their functions.

Moreover, far from total abandonment of usable elements of existing agencies and programs involved in the present fragmented health planning process, the proposal provides for an orderly transition to bring those agencies into a new alignment of Health Systems Agencies envisioned in the bill. Hill-Burton, CHP, and RMP programs would be eligible to receive technical assistance from the Department of Health, Education, and Welfare to enable them to qualify for provisional certification as a Health Systems Agency under the proposal. The provision of that assistance could be conditioned upon a reorganization of the recipient entity or its merger with another entity.

Of the health planning bills currently being considered by the Congress, with few exceptions, most can be characterized by their similarities to the Administration bill rather than their differences. It appears that somewhere in the chronology of RMP fortunes, the issue has become not whether RMP should remain or be terminated, but whether RMP is willing to shed its present nomenclature and limitations and participate in the more comprehensive approach to improving health care which is being developed today.

Refer to: California Medical Association Committee on Occupational Health: Occupational Health—Status of governmental and legal control in California (Information). West J Med 121:161, Aug 1974

Occupational Health

Status of Governmental and Legal Control in California

In 1970 the United States Congress passed the Williams-Steiger Occupational Safety and Health Act (OSHA) which gave comprehensive protection against the costs of job-related injury or disease. A Physician's Guide to the Occupational Safety and Health Act of 1972 was published in the February 14, 1972, issue of the Journal of the American Medical Association (Volume 219, page 905). Reprints may be obtained from the American Medical Association, 535 No. Dearborn Street, Chicago, Illinois 60610.

The Act preempted all duties, powers and responsibilities of the states, but it did allow for state participation in administration and enforcement of state laws if these met all federal requirements. The United States Department of Labor has adopted some 450 health standards, 20 of which were standards issued by the American National Standards Institute. The others were based on limits and values of the American Conference of Governmental Hygienists. The National Institute of Occupational Safety and Health is now preparing other criteria documents on toxic materials. Because the process is so slow and there are so many toxic materials and harmful physical agents and substances, many observers believe the preparation of documents will go on indefinitely.

California, in contrast to many states, has had an active occupational health program for many years. State legislation allowing full participation in the federal program passed in October 1973 (Cal/OSHA). Most of California's laws and regulations remain in effect—for example, the regulations governing farm workers reentering grapefields, citrus orchards and cotton fields. The regulations require medical supervision of each enterprise and physicians should know what pesticides are being used and their effects on humans. Where the federal regulations are not covered by California's regulations, or California's are not as strict as the federal, then California must make the appropriate changes or additions.

Physicians should inform themselves about the detection, treatment and reporting of occupational diseases and injuries, such as poisoning from pesticides. They should know where the poison control centers are located. New regulations, both federal and state, will require greater medical supervision of workers and more medical consultation to employers. For specific questions, the physician can obtain information from his Workmen's Compensation carrier, or the Occupational Health Section in the State Department of Health.

This article was prepared by the California Medical Association Committee on Occupational Health.

Reprint requests to: E. G. Miller, MD, California Medical Association Committee on Occupational Health, 731 Market St., San Francisco, CA 94103.

Refer to: Geis G: Compensating victims of violent crime (Information). West J Med 121:161-163, Aug 1974

Compensating Victims of Violent Crime

GILBERT GEIS, PH D, *Irvine, California*

On July 1 of this year, California effected drastic revisions in its pioneering venture into public compensation of victims of violent crimes.[1] The remodeled program will raise the maximum benefits from $5,000, the lowest figure among the ten American states which now have compensation programs,[2] to $23,000. The new California law also alters the eligibility requirement for assistance from "need" to "serious financial hardship," a somewhat more liberal standard, and one that may be defined prospectively—that is, in regard to possible depletion of resources through expenses

From the Program in Social Ecology, University of California, Irvine.

Reprint requests to: G. Geis, PhD, Program in Social Ecology, University of California, Irvine, CA 92664.

that will likely be incurred as a result of injuries.

By failing to extend aid to crime victims regardless of their financial resources, however, California bypassed the more generous (and, some would argue, more just) examples of Hawaii, Massachusetts and Washington, all of which allow reparations regardless of the claimants' resources, provided that they have not recovered the losses from other sources.

The revised California crime victim compensation program, a good deal more comprehensive than its predecessor (which had been called "iniquitious,"[3] "unfortunate,"[4] and "of slight importance"[5]), contains three provisions of special interest to physicians.

- Licensed hospitals are required to display prominently in their emergency rooms posters announcing the existence of the compensation program, and to provide information about its general provisions. Standards for the location of such display material are to be established by the State Board of Control, which is responsible for the operation of the program.
- Application forms are to be supplied to each licensed physician in the state.
- Coverage provided by the program for medical and hospital care expenses of crime victims allows a maximum of $10,000 to be paid out for injuries incurred as a result of a criminal incident, plus an additional $3,000 which may be used for job retraining necessitated through victimization. (The vocational rehabilitation clause in the California bill is unique in the nation.) An additional $10,000 of compensation is available to victims for loss of earnings.

Circulation of information about the program to doctors represents an attempt to overcome what has persistently been a problem plaguing all of the compensation efforts—the lack of adequate publicity. In California, for example, there were 100,000 violent crimes in 1972, but only 700 persons filed for compensation assistance, a small fraction of those who would have been eligible for aid even under the more restrictive conditions then in existence.

To make sure that all persons who might be benefited be informed of their rights, the bill requires that law enforcement personnel must tell victims of violent crimes about the statute and must provide application forms to persons who wish to seek aid. The Attorney General is authorized to set standards for local law enforcement agencies to follow, and he may require them to file with him a description of the procedures they have adopted to comply with the law.

Particularly noteworthy in the revised law is the provision that compensation may be accorded for injury or death at the hands of a driver who violates any of four sections of the Vehicle Code. These deal with hit-and-run behavior, felony drunk driving, misdemeanor drunk driving, and driving under the influence of narcotic drugs. Previously, California, in the manner of other jurisdictions in the United States that have compensation laws, had restricted recovery to vehicular accidents in which injury or death was the consequence of the deliberate employment of an automobile, airplane, or boat as a weapon.

Other provisions of the new compensation statute include the extension of aid to residents (rather than, as before, only to domiciliaries) of California who are injured outside the state. Attorneys' fees are set at a maximum of $500; previously, they had been 10 percent of the award, but since the maximum grant then was $5,000, an attorney could not earn more than $500 under the old law either. A minimum recoverable amount is included in the law for the first time, bringing the California victim compensation program in line in this regard with most other American jurisdictions. The minimum is set at whichever figure is lower: (a) $100; or (b) 20 percent of the victim's monthly income. The minimum award provision was included largely because of the seemingly disproportionate costs of investigating smaller claims, but if experience elsewhere holds true,[6] it may be expected to result in increased listing of inflated, fictitious amounts on application forms.

Other provisions in the new California law resemble those generally found in most American jurisdictions that have victim compensation laws. Refusal of the victim to cooperate with law enforcement officers, for example, is deemed a ground for disqualification for consideration for an award. Negligence or provocation on the victim's part also can void a claim. There are provisions in the law for payments either in lump sum or periodically, though none for the setting up of an emergency fund, such as exists in several states, to aid victims with seemingly prima facie claims who face immediate financial burdens. The state is given subrogation rights under which it can attempt to recover compensation costs from the offender. Finally, though the statute does not specifically address the matter, the law is interpreted, as are all other compensation statutes, to

allow reparations even though the offender may not have been apprehended, or brought to trial or convicted. Indeed, the victim may recover even if the offender could not be convicted because he is a minor or is mentally incompetent.

The State Board of Control will continue to operate the new compensation program. When first enacted, the program had been assigned to the State Department of Social Welfare (from 1965 to 1967). It has been said that the Department had not wanted the program and gave it unenthusiastic administration. Crime victims, it was charged, were treated with skepticism, their veracity doubted, their claims delayed in processing, and a general air of condescension shown in dealings with them.[7]

In 1967, with the transfer to the State Board of Control, the Attorney General's office took over the investigation of the bona fides of claims. When investigatory material is assembled, it is presented to the three-member board (one member is the Controller, the second the Director of General Services, and the third a person appointed by the Governor to represent the public) at bi-weekly meetings. If medical expenses are involved, the payments generally are made jointly to creditors and victims.

The new legislation was largely the product of a cooperative effort between Attorney General Evelle J. Younger and State Senator Peter H. Behr. The only opponent to the bill during the floor debate in Sacramento was Senator Clark Bradley of San Jose, who termed it "a typical example of government trying to be an insurer of everybody's business." Senator Behr argued that, unfortunately, it was the poor people who couldn't afford personal insurance, even if it were available, who are most often the victims of crimes of violence. He insisted that even under the most conservative viewpoint the government had a duty to help, and pointed out that the State of California devotes almost 200 million dollars a year to care for its prisoners, but was spending less than half a million annually on the program of victim compensation. Senator Behr got 35 coauthors for the bill in the Senate, 14 more than the majority needed to assure its passage. He suggested that its rationale take the following form:

> Actually, government is subsidizing insurance for commercial property in violence-prone areas of our state. If we can do that for property, we can surely do the same for individuals. These innocent people end up with huge medical bills and often lose their jobs and pile up large debts, then end up on some form of welfare. By simply paying some of the bills directly relating to the criminal violence against them, the state may avoid paying even more to them through welfare. It's a question of which pocket you wish to take the money from.[8]

At the moment, the national Congress is considering legislation which will provide subsidies equaling about 75 percent of their costs to states which undertake to compensate innocent victims of violent crime. The federal measure, co-sponsored by Senators McClellan and Mansfield, would allow recoverable victimization costs to go up to $50,000 under the subvention arrangements. The federal bill would also set a criterion of "financial stress" as necessary for compensation eligibility. Presumably, passage of the federal bill would result in the setting up of victim compensation programs in the remaining 40 state jurisdictions in the United States which are now without them, and, as an important byproduct, would probably result in a more intensive examination of issues of the causes and costs of crime as the physical, psychological and fiscal costs of victimization became more strikingly apparent.

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BRUCE O. BERG, MD, San Francisco, California
Director of Child Neurology, University of California Medical Center

- **Non-Convulsive Paroxysmal Disorders in Children**
- **The Child with Large Head**
- **Panel Discussion on Reye's Syndrome**

ROBERT FONTANA, MD, Rochester, Minnesota
Associate Professor of Medicine, Mayo Medical School

JOHN P. GEIGHNER, MD, San Diego, California

- **Panel on State Mental Hospitals and the Future of State Mental Health Programs**
- **Panel on Status of the Mental Health Commitment Law**

ROBERT M. HARDAWAY, III, MD, El Paso, Texas
Brigadier General, MC, Department of Army William Beaumont General Hospital

- **Pathophysiology and Treatment of Shock**
- **Disseminated Intravascular Coagulopathy**
- **Panel on Shock**

KENNETH M. MOSER, MD, San Diego, California
Professor of Medicine, Director, Pulmonary Division, University of California, San Diego, School of Medicine

G. TOM SHIRES, MD, Seattle, Washington
Professor and Chairman, Department of Surgery, University of Washington, School of Medicine

- **Initial Care of Injured**
- **Panel on Trauma**

LTC. JOHN P. SHOCK, MC, San Francisco, California
Ophthalmology Department, Letterman Army Medical Center

- **Phacofragmentation and Irrigation of Cataracts**
- **Current Status of Phacocryolysis**

MORTON A. STENCHEVER, MD, Salt Lake City, Utah
Professor and Chairman, Department of Obstetrics and Gynecology, University of Utah College of Medicine

- **The Genetics of Reproductive Failure**
- **The Prenatal Diagnosis of Genetic Diseases**
- **Panel Discussion—Ask the Experts**
- **Grand Rounds—Ob-Gyn**

in memoriam

Baldwin, L. Grant, Pasadena. Died April 20, 1974 in Pasadena of cerebrovascular accident, aged 72. Graduate of the University of Michigan Medical School, Ann Arbor, 1925. Licensed in California in 1929. Dr. Baldwin was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Bilafer, Robert A., Daly City. Died May 29, 1974 in Daly City, aged 66. Graduate of the University of Southern California School of Medicine, Los Angeles, 1934. Licensed in California in 1934. Dr. Bilafer was a member of the San Francisco Medical Society.

Brannon, Earl William, jr., Los Angeles. Died May 3, 1974 in Los Angeles, aged 53. Graduate of Western Reserve University School of Medicine, Cleveland, 1945. Licensed in California in 1970. Dr. Brannon was a member of the Los Angeles County Medical Association.

Brignoli, Walter H., St. Helena. Died May 6, 1974 in St. Helena of adenocarcinoma of the stomach, aged 63. Graduate of the University of California Medical School, Berkeley-San Francisco, 1936. Licensed in California in 1936. Dr. Brignoli was a member of the Napa County Medical Society.

Cline, John Wesley, San Francisco. Died July 10, 1974 in San Francisco of heart disease, aged 76. Graduate of Harvard Medical School, Boston, 1925. Licensed in California in 1929. Doctor Cline was a past president of the American Medical Association, of the California Medical Association, and of the San Francisco Medical Society, a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Deleray, Wilfred Louis, San Gabriel. Died May 23, 1974 of injuries received in an automobile accident near Kabul, Afghanistan, aged 64. Graduate of McGill University Faculty of Medicine, Montreal, 1939. Licensed in California in 1939. Dr. Deleray was a member of the Los Angeles County Medical Association.

DeWitt, Foster, Oakland. Died April 21, 1974, aged 48. Graduate of Universität Bern, Medizinische Facultät, 1956. Licensed in California in 1958. Dr. DeWitt was a member of the Alameda-Contra Costa Medical Association.

Draper, David H., San Bernardino. Died June 1, 1974 in San Bernardino, aged 48. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1952. Licensed in California in 1969. Dr. Draper was a member of the San Bernardino County Medical Society.

Fesenmaier, Otto Bernard, Los Angeles. Died May 19, 1974 in Los Angeles of carcinoma of the colon, aged 66. Graduate of Marquette University School of Medicine, Milwaukee, 1936. Licensed in California in 1966. Dr. Fesenmaier was a member of the Los Angeles County Medical Association.

Foster, William Paul, Arcata. Died April 21, 1974 in Arcata of cerebral edema, aged 42. Graduate of Chicago College of Osteopathy, 1960. Licensed in California in 1962. M.D. degree from California College of Medicine, 1962. Dr. Foster was a member of the Humboldt-Del Norte County Medical Society.

Frame, Paul W., sr., Sacramento. Died May 26, 1974 in Sacramento, aged 80. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1924. Licensed in California in 1924. Dr. Frame was a retired member of the Sacramento County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Frederickson, Sophie Henrietta, Glen Ellen. Died April 22, 1974 in Glen Ellen of arteriosclerotic cardiovascular disease, aged 84. Graduate of the University of Illinois College of Medicine, Chicago, 1916. Licensed in California in 1928. Dr. Frederickson was a retired member of the Sonoma County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Frizzell, Rex Russell, Pasadena. Died May 17, 1974, aged 88. Graduate of Rush Medical College, Chicago, 1911. Licensed in California in 1916. Dr. Frizzell was a member of the Los Angeles County Medical Association.

Garetz, Michael A., San Jose. Died May 8, 1974 in San Jose, aged 59. Graduate of the University of Minnesota Medical School, Minneapolis, 1940. Licensed in California in 1940. Dr. Garetz was a member of the Santa Clara County Medical Society.

Gentry, Richard W., Riverside. Died May 18, 1974 in Riverside, aged 49. Graduate of the University of California Medical School, Berkeley-San Francisco, 1947. Licensed in California in 1948. Dr. Gentry was a member of the Riverside County Medical Association.

Haddow, Norval W., Los Angeles. Died May 2, 1974 in Los Angeles of hepatic failure, aged 75. Graduate of the University of Minnesota Medical School, Minneapolis, 1923. Licensed in California in 1930. Dr. Haddow was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Hodgdon, Frank W. jr., Pasadena. Died June 7, 1974 of cancer, aged 83. Graduate of Harvard Medical School, Boston, 1916. Licensed in California in 1920. Dr. Hodgdon was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Hummel, Alvin Lee, Santa Barbara. Was killed April 28, 1974 in a plane crash near Gold Beach, Oregon, aged 38. Graduate of Loma Linda University School of Medicine, Loma Linda-Los Angeles, 1962. Licensed in Cali-

fornia in 1966. Dr. Hummel was a member of the Santa Barbara County Medical Society.

HUSBAND, MYRON, SR., Salinas. Died May 19, 1974 in Eureka, aged 75. Graduate of the University of Minnesota Medical School, Minneapolis, 1928. Licensed in California in 1948. Dr. Husband was a retired member of the Monterey County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

ISAAK-JANTZEN, CONSTANTINE JOHN, Vallejo. Died May 9, 1974 in Vallejo, aged 61. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1938. Licensed in California in 1941. Dr. Jantzen was a member of the Solano County Medical Society.

JOHNSON, ERNEST D., Alhambra. Died May 29, 1974 in Pasadena of heart disease, aged 79. Graduate of the University of Nebraska College of Medicine, Omaha, 1920. Licensed in California in 1923. Dr. Johnson was a member of the Los Angeles County Medical Association.

LEDFORD, ROY MERL, SR., San Diego. Died May 6, 1974 in Point Loma, aged 72. Graduate of the University of Illinois College of Medicine, Chicago, 1927. Licensed in California in 1927. Dr. Ledford was a member of the San Diego County Medical Society.

LUSBY, RALPH WARD, Westlake Village. Died January 14, 1974 in Westlake Village of cardiorespiratory failure, aged 79. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1916. Licensed in California in 1917. M.D. degree from California College of Medicine, 1962. Dr. Lusby was a member of the Los Angeles County Medical Association.

MISSNER, FRANK ROY, Berkeley. Died May 26, 1974 in Nevada City of heart disease, aged 86. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1917. Licensed in California in 1923. Dr. Missner was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

MOORE, OLIVER MERRITT, Bell. Died May 7, 1974 in Lynwood, aged 75. Graduate of Rush Medical College, Chicago, 1923. Licensed in California in 1923. Dr. Moore was a member of the Los Angeles County Medical Association.

MORRIS, ROY HENRY, San Francisco. Died June 16, 1974 in San Francisco, aged 91. Graduate of Cooper Medical College, San Francisco, 1905. Licensed in California in 1905. Doctor Morris was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

SABLE, MORRIS, Los Gatos. Died May 10, 1974 in San Jose of cancer, aged 51. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1955. Licensed in California in 1955. Dr. Sable was a member of the Santa Clara County Medical Society.

SKORNECK, ALAN B., San Pedro. Died April 28, 1974, aged 57. Graduate of the University of Minnesota Medical School, Minneapolis, 1944. Licensed in California in 1955. Dr. Skorneck was a member of the Los Angeles County Medical Association.

SNYDER, WILLIAM H., JR., Los Angeles. Died June 1, 1974 in Kittery, Maine, aged 69. Graduate of Harvard Medical School, Boston, 1930. Licensed in California in 1934. Dr. Snyder was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

STANGE, FREDERICK ALBERT, Torrance. Died June 4, 1974 in Torrance of cerebral vascular accident, aged 59. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1954. Licensed in California in 1955. MD degree from California College of Medicine, 1962. Doctor Stange was a member of the Los Angeles County Medical Association.

SULLIVAN, CLETUS S., San Jose. Died May 11, 1974 in San Jose, aged 72. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1926. Licensed in California in 1926. Dr. Sullivan was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

THURLOW, ALFRED A., JR., Santa Rosa. Died May 22, 1974 in Santa Rosa of subarachnoid hemorrhage, aged 57. Graduate of Washington University School of Medicine, St. Louis, 1943. Licensed in California in 1943. Dr. Thurlow was a member of the Sonoma County Medical Association.

TITCOMB, LILLIAN RAY, Los Angeles. Died May 30, 1974 in Covina of general arteriosclerosis, aged 100. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1908. Licensed in California in 1910. Dr. Titcomb was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

WARNER, OHMER HUBERT, San Diego. Died in April 1974, aged 88. Graduate of the University of Minnesota Medical School, Minneapolis, 1912. Licensed in California in 1928. Dr. Warner was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

WELLS, MARIA C., Los Angeles. Died April 27, 1974 in Beverly Hills, aged 91. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1917. Licensed in California in 1917. Dr. Wells was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

YOUNG, MAURICE LEON, North Hollywood. Died January 25, 1974 of myocardial infarction, aged 70. Graduate of the University of Illinois College of Medicine, Chicago, 1931. Licensed in California in 1931. Doctor Young was a member of the Los Angeles County Medical Association.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

VASCULAR SURGERY—Volume 1—Peripheral Arterial Diseases—John J. Cranley, MD, Director, Department of Surgery and Department of Medical Education, Good Samaritan Hospital, Cincinnati, Director, Kachelmacher Memorial Varicose Vein Clinic, Logan, Ohio, and Kachelmacher Memorial Research Laboratory for Peripheral Venous Diseases, Good Samaritan Hospital, Cincinnati, Assistant Clinical Professor of Surgery, University of Cincinnati, College of Medicine; With contributions by Charles D. Hafner, MD, Raymond J. Krause, MD, and Ernest H. Meese, MD. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1972. 282 pages, with 160 illustrations, $19.95.

Stimulated by the work of DosSantos in Portugal, 22 years ago Freeman and Wylie of San Francisco began the modern era of vascular reconstructive surgery in this country. Cranley, a disciple of Linton and Herrmann, was among the first to pick up and further develop these techniques. His experience is reflected in this book which is a sound epitome of modern vascular thinking and practice. He discusses controversial topics fairly but does not hesitate to state his own convictions based on his extensive experience. The book is a thorough introduction to the surgical treatment of peripheral arterial diseases. All the major disease entities which custom includes in this general title are thoroughly covered, with a survey of etiology, pathogenesis, abnormal physiology, diagnosis, and a brief but satisfactory outline of nonsurgical treatment. The description of the surgical approach to these conditions is concise but complete. Students, surgical residents, and members of other specialty groups will find this an excellent introduction to modern vascular surgery.

FRANK H. LEEDS, MD

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UPPERS AND DOWNERS—David E. Smith, MD, and Donald R. Wesson, MD. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1973. Available through Haight-Ashbury Publications, P.O. Box 27278, San Francisco, CA 94127. 152 pages, $2.45 plus 35¢ postage and handling. California residents add sales tax.

This is a collection of essays by professionals close to the drug scene and whose experience extends to the very birth of the Haight-Ashbury phenomenon. This effort covers the non-opioid drugs; amphetamines, barbiturates, methaqualone, and cocaine. These are keen and sensitive observations by persons completely familiar with this borderland of medical practice. The essay on the treatment of barbiturate addiction is extremely valuable from a practical standpoint. Cocaine, an old-timer, appears to be making a comeback on the illicit drug scene. It is well covered in a chapter.

Throughout the book the authors give much attention to the manufacturing and distribution of these drugs. They believe that the manufacturers are motivated by profits and that the distribution has been unacceptably careless. The prescribing habits of American physicians are critically reviewed and we are forcefully reminded that over-prescription of drugs, particularly with questionable indications, is hazardous.

With few exceptions most of the pieces include one of the editors as an author. Therefore, the collection hangs together nicely and does not suffer from the disjointed effect of many such collections.

There are two notable exceptions. The rough voice of Senator Mike Gravel gives the drug industry a thorough sandpapering for its alleged irresponsibility in the manufacture and control of drugs. The political and economic aspects of drug abuse echo through most of these essays.

Finally, Dr. Thomas S. Szasz, well-known inducer of excessive catecholamine levels in orthodox psychiatrists, offers a chapter on the ethics of addiction which proclaims that personal freedom should extend to the right of self-medication, and that drug abuse is indeed a moral rather than a medical problem. We *do* have the right to take narcotics and other drugs, says Dr. Szasz, if we conduct ourselves as law-abiding citizens. Existentialism unlimited!

JACK D. GORDON, MD

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PILLS, PROFITS, AND POLITICS—Milton Silverman, PhD, Research Pharmacologist and Lecturer in Pharmacology, University of California, San Francisco; and Philip R. Lee, MD, Professor of Social Medicine, University of California, San Francisco. University of California Press, 2223 Fulton Street, Berkeley, CA (94720), 1974. 421 pages, $10.95.

The two authors, one a former Assistant Secretary for Health, Education, and Welfare and the other a former newspaperman and now a research pharmacologist, have joined forces to produce this book. Each has an acknowledged familiarity with the subject. This book will cause ripples if not waves in the already troubled waters of the pharmaceutical industry and its relations with government. It will be read with interest by persons in or out of medicine who are interested in this subject of so much controversy. It will no doubt sell well in the present climate.

MALCOLM S. M. WATTS, MD

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MICROBIOLOGY—Second Edition—Bernard D. Davis, MD, Adele Lehman Professor of Bacterial Physiology, Harvard Medical School; Renato Dulbecco, MD, Assistant Director of Research, Imperial Cancer Research Fund Laboratories, London: Herman N. Eisen, MD, Professor of Immunology, Massachusetts Institute of Technology, Cambridge; Harold S. Ginsberg, MD, Professor and Chairman, Department of Microbiology, College of Physicians and Surgeons, Columbia University, New York; and W. Barry Wood, Jr., MD (deceased), Boury Professor and Director, Department of Microbiology, Johns Hopkins University School of Medicine, Baltimore, Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1973. 1584 pages, with 1300 illustrations, $27.50.

The first edition of this text (which appeared about 6 years ago) rapidly established itself as the most imaginatively composed book on the fundamentals of microbiology and immunology for medical students. The second edition lives up fully to the standards of the first, and perhaps even exeeds them in some areas.

The eminence of the authors can be judged by the fact that, of six names listed, five are members of the National Academy of Sciences. Since Dr. Barry Wood's untimely death, the section on bacterial and mycotic infections has been revised by Dr. McCarty with many different collaborators. While this makes for a less uniform coverage of the subjects than before, most of the sections are of very high caliber. Particular mention should be made of the comprehensive, 33-page section on Gram negative and enteric bacteria by A. Sonnenwirth.

A 280-page section on immunology by H. Eisen is probably the most lucid and sophisticated summary of knowledge in the field of fundamental immunology currently available. (This section has also been published separately as a paperback for $10.00.)

The entire book places strong emphasis on logical development of scientific knowledge in the field, rather

than an enumeration of facts. Lavishly illustrated, many parts of the book are easy to read and follow and thus present a superb introduction to microbiology, virology, immunology for medical students—if they have the time to cover the 1,584 pages in detail and with some leisure. The practicing physician will find a wealth of background information, but—at times—a paucity of readily applicable practical facts. There can be little doubt, however, that this second edition will stand for some years as the leading basic reference text in the fields presented.

ERNEST JAWETZ, MD, PH D

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SURGICAL PATHOLOGY—Fifth Edition—Lauren V. Ackerman, MD, Professor Emeritus of Surgical Pathology and Pathology, Washington University School of Medicine, St. Louis, Professor of Pathology, State University of New York at Stony Brook; and Juan Rosai, MD, Associate Professor of Pathology, Washington University School of Medicine, Associate Surgical Pathologist, Barnes and Affiliated Hospitals, St. Louis. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis (63103), 1974. 1394 pages, with 1329 figures, $45.50.

Ackerman's *Surgical Pathology* for many years has been the standard book in this field of pathology. For the fifth edition, Dr. Juan Rosai has been added as a co-author, the text has been expanded and revised, and almost all of the book has been extensively rewritten. This has resulted in a more comprehensive book which, more than ever, makes it the premier book in surgical pathology.

The references have always been one of the outstanding features of Dr. Ackerman's books, and for this edition many of the older references have been eliminated, the classic ones retained, and many new references added. The references have been carefully selected to pick the most significant articles in the field and the references are up-to-date through the middle of 1973. The references are easy to use because they are divided into the topics discussed in the text, numbered and alphabetically arranged. The book is lavishly illustrated, with an average of almost one illustration per page and most of the illustrations are of excellent quality. However, some of the illustrations are of suboptimal quality. This is surprising since a uniformly high quality of illustrations has always been one of the outstanding features of the previous editions. One would conclude that the poor photographs are the result of the publishing technique rather than the author's providing poor photographs. In spite of these difficulties, the majority of the illustrations are excellent and complement the text.

In previous editions, the text was often scant, sometimes leaving the reader wishing for more detail. The text in this edition has been greatly expanded and is ample, yet concise. The text contains excellent pathologic descriptions of most entities and the clinical-pathologic correlation is superb. The text also contains numerous "pearls" and almost every page includes advice and helpful suggestions for avoiding errors in pathologic diagnoses. In many chapters, charts and tables have been added for clarification and these are helpful. The tendency in the previous editions to mention unusual and rare lesions without further description or references has been largely overcome although a few of these are still encountered in some chapters.

As would be expected in a single volume work encompassing the vast field of surgical pathology, the specialist in various areas may find individual chapters lacking sufficient detail, or the newest concepts. For example, in the renal chapter, the IgG-IgA form of focal glomerulonephritis is not mentioned and focal glomerulosclerosis is not classified as a separate entity. In fact the kidney chapter contains only one electron micrograph. It is from a case of lupus nephritis, and does not show the osmophilic deposits and microtubular arrays characteristically found in lupus. In surgical pathology, ultrastructure is probably most helpful in the interpretation of the renal biopsy yet neither the chapter on ultrastructure nor the kidney chapter describes the ultrastructural changes in glomerulonephritis in any detail. In addition, there is little mention of the usefulness of immunofluorescence in the diagnosis of renal disease. In the ovarian chapter, the concept of tumors of borderline malignancy is discussed only briefly and criteria for their diagnosis are lacking.

In any book of this scope and size, errors are bound to be missed. For example, on page 815, in the discussion of leiomyosarcoma, the number of mitotic figures required for a diagnosis of malignancy is quoted as per "high power field" when the authors, I am sure, mean per "10 high power fields." Some statements are controversial, such as the recommendation on page 6, that bone marrow biopsies be fixed in neutral buffered formalin. Most hematopathologists consider formalin a poor fixative for bone marrow biopsies and Bouin's or Zenker's solution are usually preferred.

Overall, however, this is a superb book. The authors have achieved the almost impossible task of presenting most of the important facts in the field of surgical pathology in one amply illustrated and lavishly referenced volume which deserves to be in the library of every pathologist involved in diagnostic tissue pathology. It should be read from cover to cover by every resident in pathology and those just beginning to practice anatomic pathology. Clinicians will also find significant information in most chapters. For the more experienced pathologist there is new information in the text and the references alone are worth the purchase price of the book.

In summary, this already classic work in the field of surgical pathology has been improved, brought up-to-date and made more comprehensive. Pathologists will find it invaluable and clinicians in most specialities will find it to be of value. The book stands as a monument to the ability and wisdom of the authors, and, like the previous editions, will achieve worldwide distribution and influence.

RICHARD L. KEMPSON, MD

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DYSLEXIA—Problems of Reading Disabilities—Herman K. Goldberg, MD, Associate Professor of Ophthalmology, Wilmer Institute, The Johns Hopkins Hospital; Associate Professor of Pediatrics, The Johns Hopkins Hospital, Chief of Ophthalmology, Kennedy Institute, The Johns Hopkins Hospital, Director, Division of Ophthalmology, Sinai Hospital of Baltimore, Chief of Ophthalmology, The Good Samaritan Hospital, Baltimore; and Gilbert B. Schiffman, Ed D, Director, Division of Education, and Associate Professor of Education, Evening College and Summer School, and Assistant Professor of Special Education, Department of Pediatrics, The Johns Hopkins University, Baltimore. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1972. 194 pages, $8.75.

Goldberg and Schiffman discuss the problems of reading disabilities from several points of view: psychological evaluation, brain damage or dysfunction, peripheral and central aspects of visual perception, peripheral and central aspects of auditory perception, emotional disturbance, the role of cerebral dominance, and genetics. In addition to considering the possible etiologic relevance of brain damage, peripheral visual and auditory disability, central visual and auditory perceptual difficulties, emotional problems, and the concept of mixed dominance, the authors describe the diagnostic role of the clinical psychologist, the ophthalmologist, the otologist, the psychiatrist, and the pediatrician. There is also an excellent and very useful evaluation of the various types of treatment which have been directed against the reading disabilities over the years. In particular, considerable

space is devoted to evaluation of visual training, training directed against mixed dominance, and special educational techniques. Less space is devoted to psychiatric treatment.

The strongest and most useful material in this book is that devoted to evaluating a number of no longer acceptable etiologic notions, and treatment modes based upon these notions, which have accumulated over the years. In particular, the authors evaluate in readily understandable terms the numerous and often highly publicized attempts to deal with the reading disabilities by either visual training methods or by training procedures directed at establishing adequate cerebral dominance. The authors help the reader to come to the inevitable conclusion that both types of training have absolutely nothing whatsoever to offer to the child with a reading disability. The relative uselessness of medication is also emphasized. On the other hand, the authors point out the necessity of understanding the child's personality, his response to his reading disability, and his family's attitude toward him and his disability. Thus, they make a convincing case for considering the importance of psychiatric factors in evaluating and helping the child with a reading disability.

The authors also emphasize the importance of the proper special educational techniques in the remediation of a reading disability. However, the authors do better in describing improper educational techniques than in specifying those techniques which they feel may be useful. When the reader has finished the book he is left with a certain sense of vagueness as what he should do in respect to developing a specific treatment program for a child with a reading disability. This apparent deficiency in the book perhaps stems from the fact that the etiologies underlying the reading disabilities are in fact very poorly understood. A related difficulty in this book is that the authors are also quite inconsistent as to whether they are talking about dyslexia as a specific reading disability or as a symptom of a more general learning disability. In fact, the reader will find himself following the authors' line of reasoning in almost any chapter of this book, thinking that a particular point is being made about dyslexia and suddenly realizing that the authors have shifted from talking about, for example, psychological testing or central perceptual problems in a specific reading disability to the same issues in regard to the more general learning disabilities. In fact, several re-readings of this book leave the reviewer with the impression that the authors wrote their text without having ever decided if there really is such a thing as dyslexia defined as a specific reading disability in an otherwise normally functioning child. The greater part of the book is actually devoted to learning disabilities.

For the most part, this book is written at a level of discourse best suited for the parent or teacher of a child with a learning disorder. For example, considerable space is devoted to such issues as what an electroencephalograph is and how it works. The terms are simple and may be informative to the non-medical reader. For example, it is stated that the patterns on the EEG "indicate whether the brain is functioning normally or whether there is damage present in any particular area." Similarly, in the long chapter on the role of vision in learning, considerable space is devoted to a very simplified explanation of the anatomy of the eye which "consists of a transparent covering called the cornea. Inside of this is the iris, which gives the eye its color," and so forth. Although some sections of the book, for example, the chapter on psychological testing, provide information useful to the physician, the average physician will find a considerable part of the text rather tedious. The book is recommended therefore more for teachers and other non-medical personnel who are confronted with the child with a reading disability.

Finally, one serious omission in this book should be noted. The authors fail to identify that professional who should assume responsibility for the diagnosis and treatment or management of the child with either a specific reading or more general learning disorder. They spend considerable space in the book pointing out quite correctly how children with reading or learning disabilities can be mistreated or how time can be wasted with various specific training techniques carried out by refractionists, optometrists, psychologists, or teachers who are convinced of a particular theory and fail to diagnose adequately the child's entire problem with all of its ramifications. Clearly, these non-medical personnel should not bear the primary responsibility for diagnosis and management of these conditions (although appropriate referral to such professionals may be made for specific testing or in occasional cases, specific treatments). On the other hand, the authors point out that neither the ophthalmologist nor the pediatrician is necessarily well-equipped to deal with these problems. Obviously, the senior author of this book is an exception to that statement in that he has a long distinguished record of working with children with reading problems and his concern for these children is apparent throughout the book. This reviewer submits for consideration that the modern child psychiatrist who is trained not only in psychodynamic considerations but also to consider possible genetic, constitutional, neurologic, and neurophysiologic factors which might impair the development of perceptual and cognitive functions might be the professional who could take responsibility for the overall diagnosis and management of these conditions. This responsibility should include, however, adequate consultation with the child's pediatrician and ophthalmologist. The selection of the child psychiatrist for this responsibility seems to this reviewer to be implicit in the basic thinking about the child with a reading or learning disability which pervades the entire text. Goldberg and Schiffman repeatedly emphasize the importance of a focus on the entire child and his family including their reactions to failure, frustration, and achievement, rather than a narrow focus on the mechanics of reading or either the peripheral or central perception of the written word. The strength of this book is in this breadth of its approach to the child who cannot read and this compensates considerably for some of the ambiguities regarding the concept of a reading disability that are inherent in the text.

EDWARD M. ORNITZ, MD

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DERMATOLOGY—2nd Edition—Patrick Hall-Smith, MD (Edin), FRCP (Edin & Lond), Consultant Dermatologist, Brighton and Lewes and Mid-Sussex Groups of Hospitals; Robert J. Cairns, MB, BS (Lond), FRCP (Lond), Consultant Dermatologist, Central-Kent, Medway and Gravesend, Tunbridge Wells and Leybourne Groups of Hospitals; and R. L. B. Beare, MB, BS (Lond), FRCS (Eng), Consultant Plastic Surgeon, St. Mary's Hospital, London, Queen Victoria Hospital, East Grinstead, and Brighton General Hospital. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 374 pages, $18.50.

This is a very pleasing little book. The type is large, the editing is expertly done, the book is easy to heft, and the subsidized color plates are choice and appropriate. Even the black and white photos grab the eye. And there are many simple and informative diagrams, drawings, tables and charts. There is a useful formulary in the back. There is even a section on plastic surgery, in keeping with the present trend to include some training in this field for dermatologists. A few choice references to key articles would be a useful addition. The book is

apparently intended for the generalist in Britain, and is surprisingly broad in perspective, though inevitably lacking in depth. Converting British trade names to their American equivalents is a bit confusing, but is not too great a handicap. Cavalier recommendation of chloroquine and of chloramphenicol, for inadequate reasons, and of hexachlorphene for therapeutic purposes grates a bit on the American medical mentality. The American physician may look wistfully at the recommendation that DDT be used for perfectly adequate indications. The authors blithely ignore the Langerhans cell and the indeterminate cell in the otherwise excellent introduction. Even the American dermatologist will find much of interest in this book, such as the sections on vasculitis and the "reticuloses." For the physician who would like to be brought up to date on dermatology without encountering more than he wants to know of the subject, this is an excellent buy.

REES B. REES, MD

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TUMORS OF THE HEAD AND NECK—Clinical and Pathological Considerations—John G. Batsakis, MD, Professor of Pathology, The University of Michigan Medical Center, Ann Arbor. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1974. 388 pages, $19.75.

This book is addressed primarily to the surgical pathologist, but it may also be of interest to some ENT and head-and-neck surgeons. It deals mainly with neoplasms peculiar to the head and neck area, with some notable omissions, e.g., tumors of the thyroid and parathyroid. (As might be expected, neoplasms of the odontogenic apparatus and CNS are not included, as these subjects are usually covered in other specialty books.) In addition to neoplastic conditions, other pathologic processes which mimic tumors, i.e., cysts, proliferative lesions, and certain inflammatory states, are discussed in detail. Also, certain neoplasms which frequently involve the head and neck area but are not limited to this part of the body, e.g., lymphomas, are considered at length. The book is divided into 23 chapters, which are written by Dr. Batsakis, except for Ch. 21 (on epidermal carcinomas of the integument of the nose and ear, by Dr. John Headington) and Ch. 23 (on lymphoreticular disorders, by Drs. Bertram Schnitzer and Don Weaver).

The emphasis of this book is on the pathology of the various lesions, with comments on their behavior and a few brief remarks on treatment. The authors obviously draw from their own extensive experience, describing both relatively common entities as well as diseases rarely seen by the pathologist. The descriptions are concise and clear, and one would have little occasion to argue with their characterizations or interpretations. In general, significant areas of dispute or uncertainty in our current understanding are clearly identified. Important earlier literature of historical or basic significance is cited. The quite extensive literature on the more recent development of concepts of the pathology of the head and neck area is emphasized and covers the 1950s and particularly the decade from 1960-1970, with a few more recent references inserted. In addition to the citation of relevant articles, the contributing authors frequently add their own comments and interpretations to literature citations. The book is well written and most of the pertinent entities are well covered. Illustrations are in black and white and are average in quality, the majority depicting the microscopic aspects of disease. Thus, the book suffers from a paucity of illustrations of gross pathology or pictures of lesions as seen in the patient. Likewise, photographs of x-rays are few. The index is adequate; the printing and binding are of good quality.

In summary, this book deals with neoplasms and tumor-like conditions of the head and neck area It is well written and informative, describing both common and rare disorders. It has an extensive bibliography. Illustrations, principally photomicrographs, are of average quality with an unfortunate scarcity of illustrations of gross pathology. The book should be of considerable value to practicing surgical pathologists, particularly as a reference in dealing with uncommon conditions.

WERNER ROSENAU, MD

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DuVRIES' SURGERY OF THE FOOT—Third Edition—Editor: Verne T. Inman, MD, PhD, Professor of Orthopaedic Surgery and Director, Biomechanics Laboratory, University of California, San Francisco. Foreword by J. B. deC. M. Saunders, MD, LLD, DSC, FRCS(E), Regents Professor, University of California, San Francisco. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, MO (63141), 1973. 567 pages, $27.50.

Every physician treating disorders of the foot should read and have available a text on the foot. This third edition assures that this text will remain well accepted, reliable, and useful.

The book is primarily intended for surgeons but has much content for anyone treating foot disorders. It is not intended to be a cookbook and indeed, its organization prohibits its use in this way. Multiple authorship inevitably produces some duplication (calcanial exostoses are discussed in three separate places), but it is minimal and not objectionable. In spite of the geographic clustering of the authors, there is little recognizable provincialism. There is a significant emphasis on biomechanics, examination of the foot and etiological features of foot disorders, each welcome. The bibliography accompanying each section is superb. There are excellent sections dealing with congenital and common acquired disorders of skeletal structure, nails, and skin. Comprehensive coverage of infection, neoplasia, amputations, fractures, vascular abnormalities, metabolic abnormalities, and neuromuscular disorders are also present.

Surgical techniques are sometimes described in the text and sometimes contained in a separate section on surgical procedures. This makes it necessary for the reader to be quite familiar with the book in order to use it well. It tends to emphasize conservative and tested concepts of management with little emphasis on new techniques.

This text does not contain the scholarly and detailed historical review of operative procedures found in Kellilikian's but it is far more comprehensive. It lacks some of the expertise and explicit instructions for therapy contained in the text of Giannestras, but avoids its more dogmatic approach. It is the least expensive of these three current books dealing with the disorders of the foot.

RODNEY K. BEALS, MD

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CLINICAL GYNECOLOGIC ENDOCRINOLOGY AND INFERTILITY—Leon Speroff, MD, Robert H. Glass, MD, and Nathan G. Kase, MD, Department of Obstetrics and Gynecology, Yale University School of Medicine. The Williams & Wilkins Co., 428 East Preston Street, Baltimore (21202), 1973. 266 pages, no price given.

This is a welcome, most useful new book. It documents much recent progress but always with reference to established principles.

A new format has been chosen with large startling geometric art forms introducing numerous chapters. Excellent diagrams feature gray, black and red for interest and emphasis. Most of these are over-size, however,

and some flow-sheets take an entire page. A single (4-in.) column printing with a wide, almost empty margin to the left may bother the reader dedicated to economy of space.

A uniquely valuable review of biochemistry as the basis for endocrinology, together with a selective review of important precepts, is the introduction. Subsequent chapters feature a capsulated prospectus. The direct, almost conversational style is a refreshing change from the usual medical journalese. Only key references are included.

Reviews of hormone metabolism with "bad" as well as "good" effects are applauded. Nonetheless, tacit acceptance of an as yet admittedly unproved cause and effect sequence re: the "Pill," is regrettable. On the other hand, the "risks" of steroid contraceptives are minimized.

New (textbook) material includes transducer concepts, neurochemotransmitter factors, receptor substances and extragenital sources of hormones. Anovulation, hirsutism and dysfunctional bleeding are especially good chapters. Valuable step-wise procedures for diagnosis and treatment are provided but this is no "cook-book." Moreover, there is no implication of all-inclusive therapy.

Unfortunately, there are neither headings nor legends accompanying any of the fine illustrations. Hence the reader who is seeking specific information is impeded.

One can over-do simplification. A few clear, well-labeled photomicrographs of the endometrium would have been much more illustrative than the flashy, stylized drawings—despite color.

Five chapters dealing with aspects of infertility reveal a conservative but most successful clinical experience. Culdoscopy and laparoscopy are slighted but other surgical procedures are well covered.

Some will prefer to see the very descriptive material in the final chapter, "The Clinical Assay," integrated into earlier sections of the book.

There are definitely more "pros" than "cons" and the latter are added as friendly controversy in the hope that this fine text will be even better in the inevitable second edition. Students, house officers and generalists particularly should have this valuable book.

RALPH C. BENSON, MD

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ALIMENTARY TRACT ROENTGENOLOGY—Second Edition—Volumes 1 and 2—Edited by Alexander R. Margulis, MD, Professor and Chairman, Department of Radiology, University of California, San Francisco; and H. Joachim Burhenne, MD, Clinical Professor of Radiology, University of California, San Francisco, Chairman, Department of Radiology, Children's Hospital and Adult Medical Center, San Francisco. The C. V. Mosby Company, Publishers, 11830 Westline Industrial Drive, St. Louis (63141), 1973. 1690 pages total, in volumes 1 and 2; $100.00.

The two-volume first edition of *Alimentary Tract Roentgenology* published in 1967 is accepted as authoritative. The updated second edition follows the format of the original. Fifty-eight authors, an increase of eleven, contribute sixty-four chapters, an increase of fifteen. The number of illustrations is doubled.

Two chapters by L. P. Johnson on the physiology of gastrointestinal hormones and the mechanisms of digestion and absorption broaden the scope of the book. Other new chapters are: Abdominal Trauma (J. J. McCort), Use of Iodinated Water Soluble Contrast Agents (A. R. Margulis), Complications of Drug Therapy (J. T. Ferrucci and S. B. Eaton), Motility Disorders of the Esophagus (W. J. Dodds and G. S. Harrell), Roentgenology of Liver and Bile Ducts (A. R. Clementt), Endoscopic Camera Correlation (S. Yamagata and M. Ishikawa), Systemic Diseases Affecting the Alimentary Tract of Children (J. S. Dunbar and B. D. Fletcher) and Peroral Cholangiography and Pancreatography (J. A. Vennes).

Seven chapters are rewritten and expanded by new authors. These are: Nonneoplastic Diseases of the Stomach (W. B. Seaman), Neoplastic Diseases of the Stomach (W. Frick), Colonic Malignancy (F. E. Templeton), Infections and Infestations of the Gastrointestinal Tract (H. I. Goldberg and M. M. Reeder), Roentgenology of the Biliary Tract (H. J. Burhenne).

The section describing the biliary tract is one of the best and most extensively revised.

The index has been enlarged from 15 to 42 pages and is more detailed. Items are much easier to find.

The book is the most up-to-date and complete reference work available on alimentary tract roentgenology. It fully accomplishes the authors' goals, stated in the preface, to correct some omissions and to present a more logical sequence of chapters. It can be recommended with complete confidence to those desiring modern comprehensive accounts of subjects of radiological interest in the alimentary tract.

FREDERIC TEMPLETON, MD

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POSTOPERATIVE DISORDERS OF THE GASTROINTESTINAL TRACT—Hastings K. Wright, MD, Chief of General Surgery, Yale-New Haven Hospital, Professor and Chairman, Department of Surgery, Yale University School of Medicine, New Haven; and M. David Tilson, MD, Instructor in Surgery, Yale University School of Medicine. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 204 pages, $14.50.

This is an excellent book that I am now reading through for the second time as it contains so much useful information. I believe it should be read by every surgeon, internist, medical student and physiologist.

FRED M. ANDERSON, MD

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HUMAN RADIATION BIOLOGY—Kedar N. Prasad, PhD, Associate Professor of Radiology, Chief, Section of Radiation Biology, University of Colorado Medical Center, Denver. Medical Department, Harper & Row, Publishers, Inc., 2350 Virginia Avenue, Hagerstown, MD (21740), 1974. 524 pages, $25.00.

The book is designed for use by radiology residents and students of radiobiology. Even though the author goes into considerable detail in certain areas, the book makes easy reading. The author has devoted a major portion of the book toward the clinical side of radiation effects and has outlined various topics in each chapter, thereby facilitating ease of its use in reference.

The author initially reviews basic cell biology and along with radiation physics the current theories of biological effects. The book bogs down briefly as the author covers cellular and molecular radiation biology in great detail. The majority of the text covers radiation effects on the various organ systems and the radiation syndromes. Also discussed is the radiation hazard to the human fetus and the concept of maximum permissible dose.

The author has cogently assembled and organized a great number of facts on a difficult subject. The text's clinical orientation should make this book attractive to clinicians and anyone working in radiobiology.

CARL CARLSON, MD

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INDICATIONS: *Therapeutically*, used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

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CONTRAINDICATIONS: Not for use in the external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

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(Continued from Page 20)

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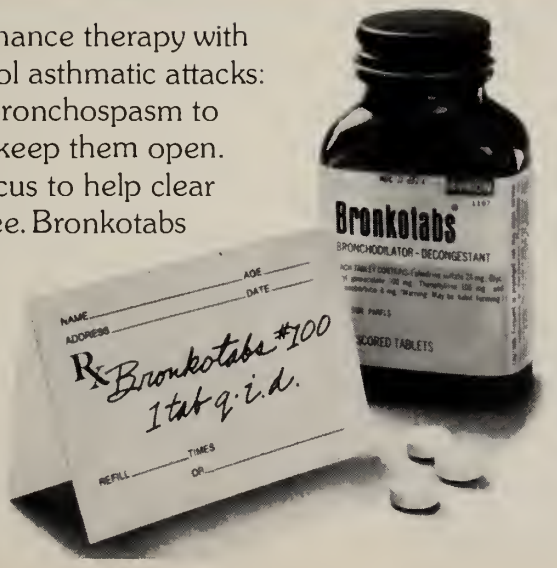

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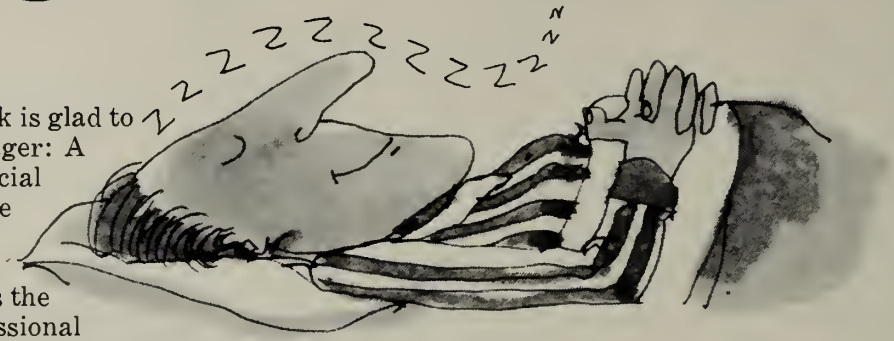

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MMITTEE ON CONTINUING MEDICAL EDUCATION

HIS BULLETIN of information regarding continuing educa-on programs and meetings of various medical organiza-ons In **California and Hawaii** is supplied by the Committee n Continuing Medical Education of the California Medical ssociation. In order that they may be listed here, please nd communications relating to your future meetings or stgraduate courses two months in advance to Committee n Continuing Medical Education, California Medical Asso-ation, 731 Market Street, San Francisco 94103; or phone 15) 777-2000. Note: Please see **California Medicine**, Vol. 17, No. 4, October, 1972 issue for a list of organizations proved for Category I Credit toward the CMA Certificate Continuing Medical Education.

NCER

ember 6-8—**Toward the Earlier Detection of Breast Can-r.** UCLA. Friday-Sunday.

ember 14—**Breast Cancer Update 1974.** American Cancer ciety, Northeast Los Angeles County Unit, at Hilton Hotel, sadena. Saturday. 6 hrs. $20. Contact: Hilario R. Liras, d. Dir., ACS, 230 N. Lake Ave., No. 1, Pasadena 91101. 13) 795-7774.

ember 27-28—**Bone Cancer: The Multidiscipline Disease.** est Coast Cancer Foundation at St. Francis Hotel, San ancisco. Friday-Saturday. $75. Contact: Jerome M. Vaeth, D, Dir., WCCF, 2200 Hayes St., San Francisco 94117.

ber 2—**Urological Cancer Conference.** American Cancer ciety and Los Angeles County Urological Society at Cen-ry Plaza Hotel, Los Angeles. Wednesday. Contact: William Tanner, Dir., Professional Ed., ACS, 2932 Wilshire Blvd., nta Monica. (213) 828-7474.

ember 11-12—**Franz Buschke Lectureship—2nd Annual.** CSF. Monday-Tuesday. Nov. 11—Heavy Particle Radia-n Therapy; Nov. 12—Hyperthermia in Cancer Therapy. ntact: Glenn E. Sheline, MD, Div. of Radiation Oncology, CSF.

ember 14-15—**Recent Advances in Hematology and Medi-l Oncology.** See Medicine, November 14-15.

ember 15-16—**Current Concepts in the Diagnosis and eatment of the Hidden Malignancies: The Intra-Abdominal ancers.** Mt. Zion Hospital and Medical Center at Fairmont otel, San Francisco. Friday-Saturday. Contact: Dept. of nt. Education, Mt. Zion Hospital, P.O. Box 7921, San ancisco 94120. (415) 567-6600, ext. 108.

tinuously—**Tumor Conference.** Cruden Education Center, . John's Hospital, Oxnard. Fridays, 12:00 noon-1:00 p.m. dvice and consultation from specialists in surgical, medical, diotherapeutic, chemotherapeutic treatment of cancer. Prac-ing physicians invited to have patients presented for dis-ssion. Cancer program has 3 year accreditation from merican College of Surgeons. Contact: D. Gordon Johnston, D, Dir. of Med. Ed., St. John's Hospital, 333 N. "F" St., xnard 93030. (805) 483-1141, ext. 266.

tinuously—**Tumor Conference.** UCSD at Pickard Audi-rium, University Hospital, San Diego. Tuesdays, 4:00 p.m. ontact: Sidney Saltzstein, MD, University Hospital, San iego. (714) 291-3330, ext. 1071.

tinuously — **Tumor Board — Harbor General Hospital.** thology Conference Room, Harbor General Hospital, Tor-nce. Fridays 3-4 p.m. Advice and consultation from spe-alists (UCLA faculty members) in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John R. Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

August 25-31—**An In-Depth Nephrology Board Review Course.** Cedars-Sinai Medical Center at Beverly Hilton Hotel, Los Angeles. Sunday-Saturday. $150. Contact: Drs. Morton H. Maxwell and Andrew J. Lewin, Div. of Nephrology & Hypertension, Mt. Sinai Hospital, 8720 Beverly Blvd., Los Angeles 90048.

September 19-21—**The Relevance of Animal Models to Human Dermato-Pharmacology and Dermato-Toxicology.** UCSF. Thursday-Saturday. 11 hrs. $200.

September 21—**Course in Armchair Allergy.** PMC. Saturday.

September 28-29—**Dermatologic Surgery.** See Surgery, September 28-29.

October 2-5—**Present Concepts in Internal Medicine.** Letterman Army Medical Center, San Francisco. Wednesday-Saturday. 24 hrs. Contact: John J. Deller, C, Dept. of Medicine, Letterman Army Med. Ctr., Presidio, San Francisco 94129. (415) 561-4275.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1975—date and place to be announced.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: Los Angeles Convention Center, Los Angeles, February 22-26, 1975.

Hawaii Medical Association—510 S. Beretania St., Honolulu 96813. Annual Meeting—Ilikai Hotel, Honolulu, October 28-November 2, 1974.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: Big Sky of Montana, Big Sky, September 12-14, 1974.

Nevada State Medical Association—3660 Baker Lane, Reno 89501. Annual Meeting: Stockmen's, Elko, September 27-29, 1974.

Oregon Medical Association—2164 SW Park Pl., Portland 97205. Annual Meeting: Hilton Hotel, Portland, September 11-15, 1974.

Washington State Medical Association—444 NE Ravenna Blvd., #108, Seattle 98115. Annual Meeting: Davenport Hotel, Spokane, September 22-25, 1974.

October 3-4—**Coronary Care.** USC. Thursday-Friday.

October 5-6—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 7-8—**Endocrine Review.** USC. Monday-Tuesday.

October 7-11—**Common Problems in Primary Care.** See Of Interest to All, October 7-11.

October 8—**Paul M. Aggeler Visiting Professor—5th Annual.** UCSF at San Francisco General Hospital. Tuesday, 11:00 a.m-12:00 noon. Judith G. Pool, Ph.D., Stanford, will talk on her research on hemophilia during a year's sabbatical at Oxford Univ. Contact: Susan Nutter, S.F. Gen. Hosp., San Francisco. (415) 648-8200, ext. 404.

October 9-11—**Symposium on Heart Disease—44th Annual.** San Francisco Heart Association at Masonic Auditorium, San Francisco. Wednesday-Friday. Contact: Lindy Abernathy, S.F. Heart Assn., 259 Geary St., San Francisco 94102. (415) 982-5753.

October 9-11—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

October 17-20—**California Society of Internal Medicine—Annual Meeting.** Ahwahnee Hotel, Yosemite. Thursday-Sunday. 8 hrs. Contact: Carol H. Handley, Exec. Dir., CSIM, 1412 Central Towers, 703 Market St., San Francisco 94103. (415) 362-1548.

October 18—**Recent Advances in Rheumatology.** UCD at Woodlake Inn, Sacramento. Friday.

October 18-19—**San Diego County Heart Association.** Sheraton-Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Mrs. Cathy Ware, Prog. Dir., SDCHA, 3640 Fifth Ave., P.O. Box 3625, San Diego 92103. (714) 291-7454.

October 19-20—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 24-26—**Non-Invasive Cardiovascular Procedures.** USC. Thursday-Saturday.

October 24-26—**West Coast Allergy Society—13th Annual Scientific Program.** St. Francis Hotel, San Francisco. Thursday-Saturday. 19 hrs. $25 for members; $30 non-members. Contact: Daniel K. Billmeyer, MD, Prog. Chr., 2164 S.W. Park Pl., Portland 97205. (503) 226-1555.

October 25—**Emergency Respiratory Care for Health Related Professions.** PMC. Friday.

October 25-26—**Clinical Gastroenterology.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. Contact: Williamson B. Strum, MD, Div. of Gastroenterology, Scripps Clinic & Research Foundation, 476 Prospect St., La Jolla 92037.

November 4-13—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

November 8—**Developments in the Diagnosis of Cont Dermatitis.** UCSF. Friday.

November 9-10—**Physiology of Respiration.** UCSF. Saturd Sunday.

November 11-15—**Pediatric Allergy and Clinical Immunolo** See Pediatrics, November 11-15.

November 14-15—**Recent Advances in Hematology and Me cal Oncology.** UCLA at Holiday Inn, Los Angeles. Thursd Friday.

November 30-December 1—**Kidney Function.** UCSF. Sat day-Sunday.

Continuously—**Review of Internal Medicine.** PMC at Pres terian Hospital, San Francisco. August 7-October 2; Wedn days, 7-10 p.m. For physicians planning ABIM recertificat exam. $25 for each session; $20 each if registered for 4 more. Aug. 7—Infectious Diseases; Aug. 14—Cardiolo Aug. 21—Neurology; Aug. 28—Hematology; Sept. 4—I phrology; Sept. 11—Pulmonary Diseases; Sept. 18—Gast enterology; Sept. 25—Rheumatology; Oct. 2—Endocrinolo

Continuously—**Recertification Review Course—Internal Me cine.** USC at Louis B. Mayer Medical Teaching Cen Keith Admin. Bldg. Tuesdays and Thursdays, 7-10 p April 9-October 10, 1974. Sessions will cover 9 broad to of internal medicine; each topic will have 5 evening sessio

Continuously—**Clinical Conferences.** Community Hospital Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospi San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Cl room. Contact: Charles H. Lithgow, MD, Dir. of Med Education, St. Mary's Hospital, 2200 Hayes St., San Fr cisco 94117. (415) 752-4000.

Continuously—**Medical Morbidity-Mortality Conference.** Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir Medical Education, St. Mary's Hospital, 2200 Hayes St., Francisco 94117. (415) 752-4000.

Continuously—**Cardiology Conference/General Medical C ference.** Cruden Education Center, St. John's Hospital, nard. Tuesdays, 12:00 noon-1:00 p.m. Conferences inclu case presentations, discussions of specific cardiology medical problems. Contact: R. E. Liguori, MD, Dir. Cardiovascular Laboratory, St. John's Hospital, 333 N. St., Oxnard 93030. (805) 483-1141, ext. 256.

Continuously—**Cardiology Conferences.** San Diego Co Heart Association at Sharp Hospital, San Diego. Fridays 10 a.m. Contact: William Kuzman, MD, Sharp Hosp 7901 Frost St., San Diego. (714) 277-6121. Or Mrs. C Ware, SDCHA, P.O. Box 3625, San Diego 92103. (291-7454.

Continuously—**Clinical Cardiology Conferences.** San D County Heart Association at University Hospital, San Di Thursdays, 8-10 p.m. Contact: Robert O'Rourke,

nstructor, Univ. Hospital, San Diego. (714) 294-5663. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

ntinuously—**Clinical Cardiology Conference.** Thursdays, :00 p.m. **Cardiosurgical Conference.** Fridays, 2:00 p.m. JCSD at University Hospital, San Diego.

ntinuously—**Medical Mortality Conference.** UCSD at Pickrd Auditorium, University Hospital, San Diego. Fridays, 1:30 a.m.

ntinuously—**Medical Chest Conference.** UCSD alternating etween University and VA Hospitals, San Diego. Thursays, 12:30 p.m.

ntinuously—**Medical-Surgical G.I. Conference.** UCSD at Jniversity Hospital, 3rd floor, rm 3, San Diego. Tuesdays, 2:30 p.m.

ntinuously—**Hematology Pathology/Hematology Morphlogy Conference.** Mondays, 11:00 a.m. **Hematology Clinical Conference.** Mondays, 12 noon. UCSD alternating between Jniversity and VA Hospitals, San Diego.

ntinuously—**Gastroenterology Conference.** Tuesdays, 11:00 .m. **Gastrointestinal Conference.** Tuesdays, 12:30 p.m. **Gasoenterology-Pathology Conference.** Wednesdays, 11:00 a.m. JCSD at University Hospital, San Diego.

ntinuously—**Renal Dialysis Traineeships.** UCSF. By special rrangement.

ntinuously—**Preceptorships in Biochemistry and Biophysics.** JCSF. By arrangement.

ntinuously—**Clinics in Dermatology.** UCSF. By arrangement.

ntinuously—**Preceptorships in Cardiology.** PMC. By arrangeent. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, ID, PMC.

ntinuously—**Preceptorships in Practical Office Dermatology.** MC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 eeks. Periods begin Oct., Jan., or April. $100. Contact: Iarold M. Schneidman, MD, Dept. of Dermatology, PMC.

ntinuously—**Preceptorships in Infectious Disease.** PMC. Full me for four weeks. To be arranged. $250. Contact: Rodney Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

ntinuously—**Renal Conference.** San Joaquin General Hosital, Stockton. First Thursday of each month, 11:00 a.m. to 2:00 noon, Conference Room 2. Contact: J. D. Kortzeborn, ID, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. 09) 982-1800.

tinuously—**Renal Conference.** UCSD alternating between niversity and VA Hospitals, San Diego. Thursdays, 12:30 m.

tinuously—**Rheumatology Conference.** UCSD at Pickard uditorium, University Hospital, San Diego. 2nd and 4th ridays, 12:30 p.m.

ntinuously—**Cardiology Conference.** San Joaquin General Iospital, Stockton. Third Wednesday of each month, 10:00-1:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, ID, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. 09) 982-1800.

tinuously—**Seminar in Clinical and Public Health Aspects f Chest Diseases.** Harbor General Hospital and CRMP Area V at Harbor General Hospital, Torrance. Three-hour sesons on second Friday of every other month, 9-12 a.m., B-3 lassroom, Chest Wards. Presentation of patients demonstrtig medical, social, and public health aspects of chest disease, ollowed by discussion of cases. Course open to physicians, urses, social workers and personnel concerned with detecon and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Iarbor General Hospital, 1000 W. Carson St., Torrance 0509. (213) 328-2380, ext. 1245.

tinuously—**Training of Physicians in Modern Concepts of ulmonary Care.** CRMP Area VI, LLU and Riverside General Iospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1534.

Continuously—**Training for Physicians in General Internal Medicine.** LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Dermatology. 11:00 a.m. VA Hospital, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

8:30 a.m., Auditorium, Brown Bldg., Mt. Sinai Hospital, Los Angeles. UCLA.

Dermatology. 10:00 a.m. University Hospital, San Diego. UCSD.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:00 noon. Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., VA Hospital, San Diego. UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:00-10:00 a.m., 4th Floor, UCLA Medical Center. UCLA.

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30-10:00 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

(Continued on Page 32)

The Role of the Detail Man

Opinion & Dialogue

"I may be prejudiced, but I am very much in favor of the detail men I meet. Most of them are knowledgeable about the drugs they promote and can be a great help in acquainting me with new medication."

Family Physician's Perception

I think that most general practitioners in this area feel as I do about the detail man. Over the years I have gotten to know most of the men who visit me regularly and they in turn have become aware of my particular interests and the nature of my practice. They, therefore, limit their discussion as much as possible to the areas of interest to me. Since I usually see the same representative again in future visits, it is in his best interest to supply me with the most honest, factual, as well as up-to-date information about his products.

Dr. Willard Gobbell
Family Physician
Encino, California

Dr. Jeremiah Stamler
Chairman
Department of Community Health and Preventive Medicine, and Dingman Professor of Cardiology
Northwestern University Medical School

"In the total picture of dealing with health problems in this country there is a potential for detail men to play a meaningful role."

The Positive Influence

My contact with representatives and salesmen of the pharmaceutical industry is the type of contact that people in a medical center, research people, and academic people have and that's in all likelihood on a somewhat different level from that of the practicing physician.

Let me touch on how I personally perceive the role of the sales representative. These men reach large numbers of health professionals. Thus they could be—and at times actually are—disseminators of useful information. They could consistently serve a real educational function in their ability to discuss their products.

At present they do distribute printed material, brochures and pamphlets—some of it scientifically sound and therefore truly useful—as well as some excellent film produced by the pharmaceutical industry. When they function in th

a Source of Information?

Yes, with certain reservations. average sales representative great fund of information t the drug products he is re- sible for. He is usually able to er most questions fully and igently. He can also supply nts of articles that contain a deal of information. Here, exercise some caution. I usu- ccept most of the statements pinions that I find in the rs and studies which come the larger teaching facilities. s without saying that a physi- should also rely on other ces for his information on macology.

ing of Sales Representatives

Ideally, a candidate for the ion as a sales representative harmaceutical company d be a graduate pharmacist has a questioning mind. I don't this is possible in every case, o it becomes the responsibility of the pharmaceutical company to train these individuals comprehensively. It is of very great importance that the detail man's knowledge of the product he represents be constantly reviewed as well as updated. This phase of the sales representative's education should be a major responsibility of the medical department of the pharmaceutical company.

I am certain that most of these companies take special care to give their detail men a great deal of information about the products they produce—information about indications, contraindications, side effects and precautions. Yet, although most of the detail men are well informed, some, unfortunately, are not. It might be helpful if sales representatives were reassessed every few years to determine whether or not they are able to fulfill their important function. Incidentally, I feel the same way about periodic assessments of everyone in the health care field, whether they be general practitioners, surgeons or salesmen.

Value of Sampling

I personally am in favor of limited sampling. I do not use sampling in order to perform clinical testing of a drug. I feel that drug testing should rightly be left to the pharmacology researcher and to the large teaching institutions where such testing can be done in a controlled environment.

I do not use samples as a "starter dose" for my patients. I do, however, find samples of drugs to be of value in that they permit me to see what the particular medication looks like. I get to see the various forms of the particular medication at first hand, and if it is in a liquid form I take the time to taste it. In that way I am able to give my patients more complete information about the particular medications that I prescribe for them.

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city they are indeed useful; cularly in the fact that they minate broadly based educa- l material and serve not just ushers" of their drugs.

ther Side of the Coin

Obviously, the pharmaceuti- mpanies are not producing all aterial as a labor of love— re in the business of selling cts for profit. In this regard mbitious and improperly moti- sales representative can a negative influence on the icing physician, both by pre- g a one-sided picture of his ct, and by encouraging the itioner to depend too heavily ugs for his total therapy. In ways, the salesman has often ted objective reality and mined his potential role as an tor.

ndustry Responsibility

Since the detail man must be ormation resource as well as resentative of his particular naceutical company, he d be carefully selected and thoroughly trained. That training, perforce, must be an ongoing one. There must be a continuing battle within and with the pharmaceutical industry for high quality not only in the selection and training of its sales representatives, but also in the development of all of its promotional and educational material.

The industry must be ready to accept constructive as well as corrective criticism from experts in the field and consumer spokesmen, and be willing to accept independent peer review. The better educated and prepared the salesman is, the more medically accurate his materials, the better off the pharmaceutical industry, health professionals and the public—*i.e.*, the patients—will be.

Physician Responsibility

The practicing physician is in constant need of up-dated information on therapeutics, including drugs. He should and does make use of drug information and answers to specific questions supplied by the pharmaceutical representative. However, that information must not be his main source of continuing education. The practitioner must keep up with what is current by making use of scientific journals, refresher courses, and information received at scientific meetings.

The practicing physician not only has the right, but has the responsibility to demand that the pharmaceutical company and its representatives supply a high level of valid and useful information. I feel certain that if such a high level is demanded by the physician as well as the public, this demand will be met by an alert and concerned pharmaceutical industry.

From my experience, my impression is that sectors of the pharmaceutical industry are indeed ethical. I challenge the industry as a whole to live up to that word in its finest sense.

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

(Continued from Page 29)

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

MENTAL RETARDATION

September 29-October 11—**Mental Retardation.** UCLA. 13 days.

OBSTETRICS AND GYNECOLOGY

September 19-21—**Biology and Pathology of Pregnancy and the Newborn Period.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Saturday.

October 9-11—**Fetal Monitoring.** USC. Wednesday-Friday.

October 12—**Prenatal Nutrition—Workshop for Physicians.** Calif. Association for Maternal and Child Health at Sheraton Inn, San Diego. Saturday. Contact: Carol G. Corruccini, M.S., 425 University Ave., No. 6, Davis 95616. (916) 756-8471.

October 14-15—**New Horizons in Perinatal Intensive Care.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. 13 hrs. $125. Contact: Bonnie Stapleton, Cont. Ed. Coord., Harbor Gen. Hosp., 1124 W. Carson, Torrance 90502. (213) 775-7711, ext. 1373.

October 16-19—**Ob-Gyn Review.** USC. Wednesday-Saturday.

October 20-23—**International Family Planning Research Association.** Gene Autry Hotel, Palm Springs. Sunday-Wednesday. Contact: Ludwig Lauerhass, Exec. Dir., 2960 W. 8th St., Los Angeles 90005. (213) 386-1970.

November 1—**Advances in Perinatal Care.** Northern California Obstetrical & Gynecologic Society at Host Airport Hotel, Sacramento. Friday. Contact: Solon Barbis, MD, Prog. Chr., 1816 Professional Dr., Sacramento. (916) 482-6510.

November 6-9—**American College of Obstetricians & Gynecologists, District VIII.** Century Plaza Hotel, Los Angeles. Wednesday-Sunday. Will reconvene Nov. 11-13 at Princess Hotel, Acapulco. Contact: ACOG District VIII, 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

Continuously—**Ob-Gyn Case Review.** Saturdays, 8:00 a.m. **Gyn Tumor Conference/Mortality Conference.** Wednesdays, 12:30 p.m. **Ob-Gyn Pathology Conference.** Wednesdays, 4:00 p.m. UCSD at University Hospital, San Diego.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

8:00-9:00 a.m., Fourth Floor Auditorium, UCLA Medical Center. UCLA.

5:00 p.m. Pickard Auditorium, University Hospital, San Diego. UCSD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Cent UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Ange County-USC Medical Center, Los Angeles. USC.

PEDIATRICS

September 11-12—**Brennemann Memorial Lectures—31st A nual.** Los Angeles Pediatric Society at Sportsmen's Lod North Hollywood. Wednesday-Thursday. Contact: Mrs. E Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (21 757-1198.

September 13-14—**Endocrinology in the Pubescent and A lescent.** Children's Hospital Medical Center, Oakland, Highlands Inn, Carmel. Friday-Saturday. 8 hrs. $50. Conta Inetta Carty Calori, Children's Hosp. Med. Ctr., 51st Grove Sts., Oakland 94609. (415) 654-5600.

October 7-11—**Common Problems in Primary Care.** See Interest to All, October 7-11.

October 14-15—**New Horizons in Perinatal Intensive Care.** S Obstetrics and Gynecology, October 14-15.

October 19-23—**American Academy of Pediatrics.** Hilt Hotel, San Francisco. Saturday-Wednesday. Contact: Rob G. Frazier, MD, Exec. Dir., 1801 Hinman Ave., Evanst Ill. 60204.

November 11-15—**Pediatric Allergy and Clinical Immunolo** UCSF. Monday-Friday.

Continuously—**Perinatal Conference.** Earl and Loraine Mil Children's Hospital, Long Beach. Fridays, 12:30 p.m., C ference Room. Contact: Marguerite Markarian, MD, Dir. Nurseries, Memorial Hospital Medical Center, 2801 Atla Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Lora Miller Children's Hospital, Long Beach. Fridays, 8:00 a. Conference Room "H." Contact: Harry W. Orme, MD, M Dir., Memorial Hospital Medical Center, 2801 Atlantic A Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arran ment.

Continuously—**Pediatric Cardiology Conference.** UCSD. Sm Conference Room, University Hospital, San Diego. Frida 12:30 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaq General Hospital, Stockton. Wednesdays, 10:00-11:15 a. and Fridays, 9:30-11:00 a.m., Conference Room 3. Conta J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Ho Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaq General Hospital, Stockton. Third Thursday of each mo 9:30-11:00 a.m., Conference Room 2. Contact: J. D. Kor born, MD, Med. Dir., San Joaquin Gen. Hosp., Stock 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vince Hospital, Los Angeles. Fourth Thursday of each month, 2 p.m., Main Doheny Conference Room. Contact: Leonard Linde, MD, Chief, Pediatric Cardiology, St. Vincent's H pital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Med Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. C tact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai M Center, 4833 Fountain Ave., Los Angeles 90029. (213) 9111, ext. 181.

Continuously—**Pediatric Immunology and Allergy Semi** UCSD. Wednesdays, 8:00 a.m.

Continuously—**Pediatric Neurology.** UCSD at University H pital, 3rd floor, rm. 3, San Diego. 1st and 3rd Wednesd 12:30 p.m.

ıtinuously—**Pediatric-Radiology-Urology Conference.** UCSD t University Hospital, Radiology Conference Room, San)iego. 1st and 3rd Fridays, 4:00 p.m.

nd Rounds—Pediatrics

'uesdays

Pediatric Cardiology. 7:30 a.m. University Hospital, San Diego. UCSD.

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Pediatric Infectious Disease. 1:30 p.m. University Hospital, San Diego. UCSD.

/ednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

hursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

ridays

8:30 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., 5th floor Ward, St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

SCHIATRY

)ber 24-27—**American Academy of Child Psychiatry.** Fairont Hotel, San Francisco. Thursday-Sunday. Contact: merican Academy of Child Psychiatry, 1800 R Street, NW, 'ashington, D.C. 20009.

ctinuously—**Adolescent Case Review.** St. Mary's Hospital, n Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conferce Room. Contact: Charles H. Lithgow, MD, Dir. of Medi-l Education, St. Mary's Hospital, 2200 Hayes St., San Fran-sco 94117. (415) 752-4000.

ctinuously—**Seminar in Ambulatory Methods.** UCSD at ental Health Clinic, San Diego. Mondays, 11:00 a.m.

ctinuously—**Preceptorships in Psychiatry.** UCSF. By arngement.

ınd Rounds—Psychiatry

ıesdays

8:30 a.m. VA Hospital, Rm. 2010, San Diego. UCSD.

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

RADIOLOGY AND PATHOLOGY

September 22-23—**Society for Pediatric Radiology.** Hilton Hotel, San Francisco. Sunday-Monday. Contact: John P. Dorst, MD, Johns Hopkins Hospital, Baltimore, Md. 21205.

September 24-27—**American Roentgen Ray Society.** Hilton Hotel, San Francisco. Tuesday-Friday. Contact: Ted F. Leigh, MD, Emory University Clinic, Atlanta, Ga. 30322.

October 25-26—**Society of Nuclear Medicine, Northern & Southern California Chapters—Annual Meeting.** Hilton Hotel, San Francisco. Friday-Saturday. Contact: Society of Nuclear Medicine, No. Calif. Chapter, 1595 Soquel Dr., Santa Cruz. (408) 476-7300.

November 2—**Laboratory Evaluation of Thyroid Diseases.** PMC. Saturday.

November 9-10—**Adult Cardiac Radiology.** UCLA. Saturday-Sunday.

November 11-12—**Franz Buschke Lectureship.** See Cancer, November 11-12.

November 16-17—**American Association for Electromyography and Electrodiagnosis.** St. Francis Hotel, San Francisco. Saturday-Sunday. Contact: W. C. Wiederholt, MD, Sec., 7010 Via Valverde, La Jolla 92037. (714) 459-8443.

Continuously—**Nuclear Medicine Conference.** Radiology Classroom, St. John's Hospital, Oxnard. Mondays, 12:00 noon-1:00 p.m. Cases reviewed and discussed. Advice and consultation from specialists in the practice of nuclear medicine techniques. Contact: Michael Lopiano, MD, Dir. of Nuclear Med. Dept., St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 297.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward I. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis

of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Continuously—**Medical X-Ray Conference.** Monday-Friday, 9:30 a.m. (Wednesdays, 8:30 a.m.). **Diagnostic X-Ray Review.** Wednesdays, 3:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Radiology/Pathology Conference.** UCSD at University Hospital, Pickard Amphitheatre, San Diego. Thursdays, 12:30 p.m.

Continuously—**G.I. Radiology Conference.** Fridays, 1:00 p.m. **Pediatric Radiology Conference.** Thursdays, 4:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Neuroradiology Conference.** UCSD at University Hospital, San Diego, Tuesdays, 4:30 p.m. and at VA Hospital, San Diego, Wednesdays, 2:00 p.m.

Continuously—**Ortho-Radiology Conference.** UCSD at VA Hospital, San Diego. Fridays, 8:00 a.m.

Continuously—**Radiology-Urology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 3:30 p.m.

Continuously—**Pathology Review.** Wednesdays, 9:30 a.m. **Cardiovascular Pathology Conference.** Tuesdays, 8:00 a.m. **Pathology-Urology Conference.** Alternate Mondays, 4:30 p.m. UCSD at University Hospital, San Diego.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

August 15-16—**Ophthalmic Skills.** PMC at Univ. of the Pacific Dental School, San Francisco. Thursday-Friday.

September 10-13—**Life Saving Measures for the Critically Injured.** See Of Interest to All, September 10-13.

September 12-13—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

September 21—**Orthopaedic Surgery and Surgical Anatomy of the Spine.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital, L.A. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Ed. Committee, ICS, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

September 26-28—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

September 26-28—**Cerebral Palsy—New Perspectives.** American Academy for Cerebral Palsy at Children's Hospital at Stanford. Thursday-Saturday. $75. Contact: E. E. Bleck, M Children's Hospital at Stanford, 520 Willow Rd., Palo A 94304.

September 26-28—**The Neck.** American Academy of Or paedic Surgeons. Anaheim. Thursday-Saturday. $150 for p sicians; $50 residents. Contact: E. Shannon Stauffer, M Rancho Los Amigos Hospital, Downey 90242.

September 28-29—**Dermatologic Surgery.** UCSF. Saturday-S day.

October 5-12—**Western Orthopedic Association.** Hawaii. week. Contact: Ms. H. Jacqueline Martin, Exec. Sec., W 354 21st St., Oakland 94612.

October 17-18—**Phaco-Fragmentation.** UCSF. Thursday- day.

October 17-19—**Phaco-Emulsification.** St. John's Hospital Southern Calif. Lions Eye Institute at St. John's Hosp Santa Monica. Thursday-Saturday. Contact: Robert M. skey, MD, 2222 Santa Monica Blvd., Santa Monica 9040

October 19—**Surgical Anatomy and Surgery of Total Hip placement.** International College of Surgeons, U.S. Sectio Los Angeles Orthopaedic Hospital, L.A., Saturday. 8 $50. Contact: Irving Rehman, PhD, Chr., Postgraduat Ongoing Ed. Committee, ICS, 5351 Tampa Ave., Tar 91356. (213) 344-3305.

October 31-November 1—**Strabismus.** PMC at Fairmont H San Francisco. Thursday-Friday.

November 9—**Orthopaedic Surgery and Surgical Anatom the Lower Extremity.** International College of Surgeons, Section, at Los Angeles Orthopaedic Hospital, L.A., S day. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., I graduate & Ongoing Ed. Committee, ICS, 5153 Tampa A Tarzana 91356. (213) 344-3305.

November 14-15—**Phaco-Fragmentation.** UCSF. Thurs Friday.

November 14-16—**Phaco-Emulsification.** St. John's Hos Santa Monica. Thursday-Saturday. Contact: Robert Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90

November 16-17—**American Society of Anesthesiologi Regional Refresher Course.** Riviera Hotel, Palm Spr Saturday-Sunday. Contact: ASA, 515 Busse Highway, Ridge, Ill. 60068.

November 21-23—**Management of Acute Hand Injuries.** and American Academy of Orthopaedic Surgeons at U Thursday-Saturday. Contact: USC or Arthur H. Osb MD, 3314 Rancho Rio Bonita Rd., Covina 91724.

November 24—**Clinical Disorders of the Pelvis.** UCLA Granada Hills Hospital at Calif. State Univ., Northr Sunday. Contact: Rose Degraffenreid, Granada Hills pital, Granada Hills. (213) 360-1021, ext. 730.

Continuously—**Anesthesia Lecture Series.** UCSD at Unive Hospital, 3rd floor conference room, San Diego. We days, 4:45 p.m.

Continuously—**Anesthesiology Mortality and Morbidity ference.** UCSD at VA Hospital, Rm. 6006, San D Thursdays, 4:30 p.m.

Continuously—**Neurological Sciences.** St. Francis Hos Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of r logical evaluations and pathological specimens of cu material and review of current topics in specialty. W notification of cases available. Contact: Ralph Miller, min. Asst., St. Francis Hospital, 3630 Imperial Hig Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Science Lecture Series.** Dept. of Su St. Mary's Hospital, San Francisco. Mondays, 11:15 12:15 p.m., Morrissey Hall. Contact: Charles H. Lit MD, Dir. of Medical Education, St. Mary's Hospital, Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. graduate traineeships of 4-14 days duration, as you wis

tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

ntinuously—**Orthopedic Lecture Series.** Alternately at St. Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser San Francisco, and Harkness Memorial Hospitals. Third Tuesday of each month, 6:00 p.m. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ntinuously—**Orthopedic Trauma Conference.** USC at Los Angeles County-USC Medical Center. Mondays, 7:00-9:00 p.m. Contact: Dept. of Orthopedics, USC School of Med., 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

ntinuously—**Preceptorships in General Surgery.** UCSF. By arrangement.

ntinuously—**Preceptorships in Neurological Surgery.** UCSF. By arrangement.

ntinuously—**Preceptorships in Urology.** UCSF. By arrangement.

ntinuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

ntinuously—**Surgical Anatomy.** St. Mary's Hospital, San Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Classroom. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ntinuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ntinuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

ntinuously—**Surgical Mortality and Morbidity Conference.** UCSD alternating between University and VA Hospitals, San Diego. Saturdays. 9:30 a.m.

ntinuously—**Ortho Surgical Conference.** UCSD at University Hospital, 3rd floor conference room, San Diego. Wednesdays, 8:00 a.m.

ntinuously—**Otolaryngology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Fridays, 8:30 a.m.

ntinuously—**Laryngeal Physiology.** UCSD at VA Hospital, San Diego. Fridays, 8:30 a.m.

ntinuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

ntinuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ntinuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ntinuously—**Trauma Conference.** UCSD at University Hospital, 1st floor conference room, San Diego. Tuesdays, 3:30 p.m.

ntinuously—**Vascular Surgery Conference.** UCSD alternating between VA and University Hospitals, San Diego. Thursdays, 4:00 p.m.

ntinuously—**Radiology-Urology Conference. Pathology-Urology Conference.** See Radiology and Pathology, Continuously.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Lebanon Hall Auditorium, Cedars-Sinai Hospital, Los Angeles. UCLA.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery.** 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Otolaryngology. 12:00 noon. University and VA Hospitals, San Diego. UCSD.

Neurology, Neuropathology, Neurosurgery. 4:00 p.m. University and VA Hospitals, San Diego. UCSD.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital, 1st, 3rd, 5th Sat.; VA Hospital, 2nd, 4th Sat., San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

August 17-28—**Postgraduate Refresher Course—17th Annual.** USC at Hawaii. 12 days. $225.

August 21-25—**Family Practice Refresher Course.** UCLA and Santa Monica Med. Center at Beverly Hilton Hotel, Los Angeles. Wednesday-Sunday.

August 25-30—**Family Practice Refresher Course.** UCD at Squaw Valley. Sunday-Friday.

August 26-30—**Computer Applications in Medical Practice—A Guided Tour.** USC Schools of Medicine and Engineering. Monday-Friday. $375. Contact: Dir. of Continuing Engineering Education, USC, Powell Hall 212, Code D, University Park, Los Angeles 90007.

September 3-8—**Family Practice Review Course—5th Annual.** UCI. Tuesday-Sunday. 44 hrs.

September 9-13—**Emergency Medicine.** UCSF. Monday-Friday.

September 10-13—**Life Saving Measures for the Critically Injured.** UCLA. Tuesday-Friday.

September 12-14—**Emergency Care.** UCSF. Thursday-Saturday.

September 20—**The Role of Nutrition in Medicine.** UCD. Friday.

October 3-5—**American Medical Writers Association—34th Annual Meeting.** Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. Contact: American Medical Writers Assn., 9650 Rockville Pike, Bethesda, Md. 20014.

October 7-11—**Primary Care.** STAN. Monday-Friday. A review course for general practitioners, family practitioners, gen. internists and gen. pediatricians.

October 10-12—**Western Industrial Health Conference—18th Annual.** Western Industrial Medical Association at Hilton Hotel, Los Angeles. Thursday-Saturday. Contact: Mr. B. H. Bravinder, Exec. Sec., P.O. Box 201, Alamo 94507. (415) 837-0874.

October 12—**Hypertension.** USC. Saturday.

October 14-17—**American Academy of Family Physicians—Annual Scientific Assembly.** Los Angeles Convention Center. Monday-Thursday. Contact: Edward E. Daleske, Sec., Comm. on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, Mo. 64114. (816) 333-9700.

October 23—**Ethical Aspects of Experimentation with Human Subjects.** USC. Wednesday.

October 28-November 1—**Intensive Care.** STAN. Monday-Friday.

October 28-November 2—**Hawaii Medical Association.** Ilikai Hotel, Honolulu. Monday-Saturday. Contact: Mr. H. Tom Thorson, Exec. Dir., 510 S. Beretania St., Honolulu 96813.

November 1-2—**Thy Brother's Keeper.** USC. Friday-Saturday.

November 10-13—**California Academy of Family Physicians.** Hyatt Regency Hotel, San Francisco. Sunday-Wednesday. Contact: William W. Rogers, Exec. Sec., CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 11-22—**Emergency Department Medicine in Practice.** Harbor General Hospital, UCLA, American College of Emergency Physicians at Harbor General Hospital, Torrance. Two weeks. $450. Contact: Mrs. Bonnie Stapleton, Cont. Ed. Coord., Professional Staff Assn., Harbor Gen. Hosp., 1124 W. Carson St., Torrance 90502.

November 17-22—**American Congress of Rehabilitation Medicine.** St. Francis Hotel, San Francisco. Sunday-Friday. Contact: Creston C. Herold, Exec. Dir., ACRM, 30 N. Michigan Ave., Chicago 60602.

November 18—**Association of Academic Physiatrists.** St. Francis Hotel, San Francisco. Tuesday. Contact: George H. Kraft, Sec., Dept. of Rehabilitation Medicine, Univ. of Washington, Seattle 98195.

November 29-December 1—**International College of Applied Nutrition—Fall Seminar.** International Hotel, Palm Springs. Friday-Sunday. Contact: Michael Walczak, MD, P.O. Box 386, La Habra 90631. (213) 697-4576.

Continuously—**Emergency Care.** USC. September 17-December 3. Tuesdays, 7:30-10:00 p.m.

Continuously—**Bedside Clinics.** USC. September 26-December 19. Thursdays, 7:30-9:30 p.m.

Continuously—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. October 1-December 3. Tuesdays (except Nov. 5 and 12).

Continuously—**Clinical Conferences.** UCSF at Community Hospital, Santa Cruz. October 9, 1974-June 11, 1975. Wednesdays.

Continuously—**Continuing Medical Education Noon Conferences.** The Hospital of the Good Samaritan, Los Angeles. Every weekday, 12-1 p.m. For monthly calendar, contact: Janie Sternal, Coord., Cont. Med. Ed., Hosp. of the Good Samaritan, 1212 Shatto St., Los Angeles 90029. (213) 48 8111.

Continuously—**Clinical Problems in Daily Practice: Physiolo cal Basis and Practical Management.** UCSF at Chinese H pital, San Francisco. 1st Tuesday of each month; 8:00-9: p.m. Aug.—Congestive Heart Failure; Sept.—Jaundice; O & Nov.—to be announced.

Continuously—**Emergency Room Lecture Series.** UCSD at U versity Hospital, San Diego. Wednesdays, 10:00 a.m.

Continuously—**Endocrinology, Metabolism, Reproductive M icine, Genetics Conference.** UCSD alternating between U versity and VA Hospitals, San Diego. Wednesdays, 11:30 a.

Continuously—**Preceptorships in International Health, Mic biology, Pharmacology and Experimental Therapeutics, P siology.** UCSF. By special arrangement.

Continuously—**Family Health Program—Southern Californ** 2925 N. Palo Verde, Long Beach. Second Friday of ea month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardi Chapter, American Academy of Family Physicians and U at Ram's Horn Inn, San Bernardino. 3rd Thursday of ea month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange Cou Chapter, American Academy of Family Physicians at Sadd back Inn, Santa Ana. 2nd Monday of each month, 7:30 p. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anahe Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Com Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Com Hosp., Baldwin Park; Huntington Intercomm. Hosp., Hu ington Beach; Imperial Gen. Hosp., Inglewood; La Hal Comm. Hosp.; La Mirada Comm. Hosp.; La Palma Int community Hosp., La Palma; Los Alamitos Gen. Hosp.; M sion Comm. Hosp., Mission Viejo; Palm Harbor Hos Garden Grove; Riviera Hosp., Torrance; Rio Hondo Me Hosp., Downey; San Gabriel Valley Comm. Hosp., S Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Ho Norwalk; West Anaheim Gen. Hosp.; Westminster Com Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterv State Hospital. Contact: Frank McCarry, MD, P.O. 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Cen** PMC and Sonoma Valley Hospital at Sonoma Valley H pital, Sonoma. Second Monday of each month in Din Room of the hospital, 8:00-10:00 p.m. $100 per series, per session. Contact: William J. Newman, MD, P.O. Box Sonoma 95476. (707) 996-3621.

Continuously—**Basic Science Seminar.** UCSD Wednesd 9:15 a.m., University Hospital of San Diego County, Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit s sidiary of CMA. Twice-a-month tape recorded summaries leading national meetings and surveys of current literat Services by subscription in: Family Practice, Surgery, ternal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesth ology, Ophthalmology, Otorhinolaryngology. Catalog of tures and panel discussions in all areas of medical prac also available. $75 per year. Contact: Mr. Claron L. Oak Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90 (213) 483-3451.

Continuously—**Medical Media Network.** Programs and st guides produced in association with faculties of major m cal schools and centers throughout the U.S. MMN ministered by University Extension, UCLA. Rental or chase, 16 mm, super 8 mm, videotape and video-cass Provides physicians with current educational programs. C tact: Ms. Jan MacAllister, Distribution Mgr., MMN, 10 Le Conte Ave., Room 540, Los Angeles 90024. (213) 7781.

Continuously—**Stanford-Mills Memorial Hospital Contin Education Program.** STAN at Mills Memorial Hospital, Mateo. Tuesday-Friday weekly. Basic Science for the C cian, Grand Rounds, Intensive Care. Contact: STAN.

)REGON

)UNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

ptember 11-15—**Oregon Medical Association 100th Annual Session.** Portland Hilton Hotel. Contact: James Kronenberg, Associate Executive Director, OMA, 2164 SW Park Place, Portland 97205.

BSTETRICS AND GYNECOLOGY

tober 6-10—**Pacific Coast Obstetric and Gynecological Society,** Bend. Contact: M. W. Breese, MD, 1133 SW Market Street, Portland 97205.

SRGERY

tember 27-October 3—**International College of Surgeons, Western Hemisphere Congress,** Portland. Contact: M. L. Brodney, 1516 N Lake Shore Drive, Chicago, IL 60610.

C INTEREST TO ALL PHYSICIANS

gust 16-17—**John Tomlin Memorial Cancer Lectures,** Rogue Valley Country Club, Medford. 12:30-5:00 pm, Friday; :00 am-1:00 pm, Saturday. Contact: American Cancer Society, Oregon Division, Inc., SW Area Unit, Box 698, 12 Leverette Building, Medford 97501

ober 16-19—**American Society of Human Genetics,** Portand. Contact: W. E. Nance, MD, Medical Genetics, Indiana University Medical Center, Indianapolis, IN 46202.

vember 30-December 4—**American Medical Association Clinical Meeting,** Portland. Contact: Ernest B. Howard, MD, AMA, 535 N. Dearborn Avenue, Chicago, IL 60610.

ASHINGTON, MONTANA, LASKA and IDAHO

tember 12-14—**Montana State Medical Association Annual Meeting.** Big Sky of Montana, Big Sky. Contact: G. Brian ins, Executive Director, MSMA, 2021 11th Avenue—Suite 2, Helena 59601. (406) 443-4000.

tember 22-25—**Washington State Medical Association Annual Meeting.** Davenport Hotel, Spokane. Contact: Harlan . Knudson, Executive Director, WSMA, 444 NE Ravenna oulevard—#108, Seattle 98115. (206) LA 3-9110.

order to have future activities listed here or to receive formation on these and other activities, please write Ms. an M. Kelday, Information Specialist, Continuing Medical ducation, WAMI Program, University of Washington School f Medicine, E-301, Health Sciences Building, SC-45, eattle, Washington 98195. Phone: (206) 543-6995.

e 12-August 28—**Expo '74—Topics in Medicine.** Every Wednesday morning for 12 weeks. Deaconess Hospital, pokane. 3 hrs. per session. $10 per session; $90 for 12 sessions. Contact Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305, HSB, SC-50, Seattle 8195. (206) 543-1050.

ust 20-25—**Northwest Protologic Society.** Tuesday-Sunday. pokane. Contact: Edward Clanton, MD, West 904 Bishop ourt, Spokane 99204.

tember 13-14—**Clinical Cancer Conference.** Friday-Saturday. Edgewater Inn, Seattle. 13 hrs. $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 13-14—**Ophthalmology for the Non-Ophthalmologist.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext 470.

September 27-28—**Arthritis Days '74.** Friday-Saturday. Seattle. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 7-11—**University of Washington School of Medicine's Eastern Circuit Course.** Moscow, Id., 7; Walla Walla, Wash., 8; Tri-Cities, Wash., 9; Yakima, Wash., 10; Wenatchee, Wash., 11. Fee not set. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305, HSB, SC-50, Seattle 98195. (206) 543-1050.

October 24-25—**Office Management of Chronic Pain.** Seattle. Fee not set. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305, HSB, SC-50, Seattle 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

Ayerst Laboratories
Premarin 10, 11

Bio-Science Laboratories
Laboratory Service ..... 4th Cover

Breon Laboratories Inc.
Bronkotabs 25

Burroughs Welcome Co.
Neosporin Ointment 23

Classified 20, 24

Compton Foundation 20

Dorsey Laboratories
Triaminic Expectorant 3
Triaminic Syrup 17

Lakeside Laboratories, Inc.
Norpramin 4, 5

Eli Lilly and Company
Ilosone Liquid 250 22

Mead Johnson Laboratories
Vasodilan 9

Marsh & McLennan, Inc.
CMA Insurance 13

Pharmaceutical Manufacturers Association
Prescription Ads 30, 31

Presto Food Products Inc.
Matey 21

Roche Laboratories
Dalamane ..... 2nd Cover and Page 1
Bactrim 6, 7, 8
Librium 14, 15

G. D. Searle & Co.
Pro-Banthine ..... 38 and 3rd Cover

Security Pacific Bank 26

State Compensation Insurance Fund 16

Stanford University
Primary Care 12

Wyeth Laboratories
Bicillin/Wycillin 18, 19

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*Fordtran, J. S., and Collyns, J. A. H.: Antacid Pharmacology in Duodenal Ulcer: Effect of Antacids on Postcibal Gastric Acidity and Peptic Activity, New England J. Med. 274:921-927 (April 28) 1966.

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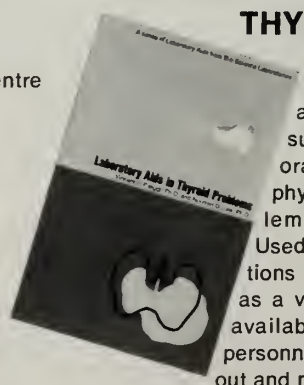

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THE WESTERN Journal of Medicine

VOLUME 121 • NUMBER 3 **SEPTEMBER 1974**

173 *Superinfections of the Lung—An Evaluation for Serial Transtracheal Aspirations*
E. JACK BENNER, MD, JURG P. MUNZINGER, MD, and RICHARD CHAN, MD

179 *Neutrophilic Hypersegmentation Without Macrocytic Anemia*
PAUL G. HATTERSLEY, MD, and JUDITH L. ENGELS, MT

185 *Adenocarcinoma of the Colon and Rectum* ALLAN J. WAGMAN, MD, and WILLIAM H. KERN, MD

MEDICAL PROGRESS

188 *Parkinson's Disease and Levodopa—A Five-Year Follow-up and Review*
CHARLES H. MARKHAM, MD, LEO J. TRECIOKAS, MD, and SHIRLEY G. DIAMOND, BA

SPECIALTY CONFERENCE

207 *Brain Abscess*
Moderator: THOMAS T. YOSHIKAWA, MD; Discussants: STANLEY J. GOODMAN, MD, and THOMAS T. YOSHIKAWA, MD
Teaching Conference in Infectious Diseases, UCLA School of Medicine, Harbor General Hospital, Torrance

220 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*General Surgery*

228 EDITORIALS • *Levodopa After Five Years* • *Duty to Report Child Abuse* • *Brain Abscess* • *Reaching the Unreached with Health Care*

CASE REPORT

232 *Evidence of Skeletal Muscle Involvement in Psittacosis* PETER SULLIVAN, MD, and AUSTIN BREWIN, MD

235 LETTERS TO THE EDITOR

TRAUMA ROUNDS

240 *Management of Pancreatic Injuries* Chief Discussant: MURIEL STEELE, MD

MEDICAL JURISPRUDENCE

244 *Malpractice Liability for Failing to Report Child Abuse* RICHARD J. KOHLMAN, Esq.

HEALTH CARE TEAM

249 *Group Practice Approach to Rural Community Mental Health* NOEL GUILLOZET, MD

AN INFORMED COMMENTARY

254 *Medical Manpower in Oregon* ALEXANDER R. GASSAWAY, PhD

INFORMATION

261 *Chinese Herbal Medicines* FDA Drug Bulletin—July 1974

263 *In Memoriam*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON, MONTANA, ALASKA, AND IDAHO**
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For further information on this subject, the following references are provided:

1. Henry BW, *et al: Dis Nerv Syst 30*:675-679, Oct 1969.
2. Hollister LE, *et al: Arch Gen Psychiatry 24*:273-278, Mar 1971.
3. Claghorn J: *Psychosomatics 11*:438-441, Sept-Oct 1970.

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in psychoneurotic anxiety states with associated depressive symptoms

surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

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The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

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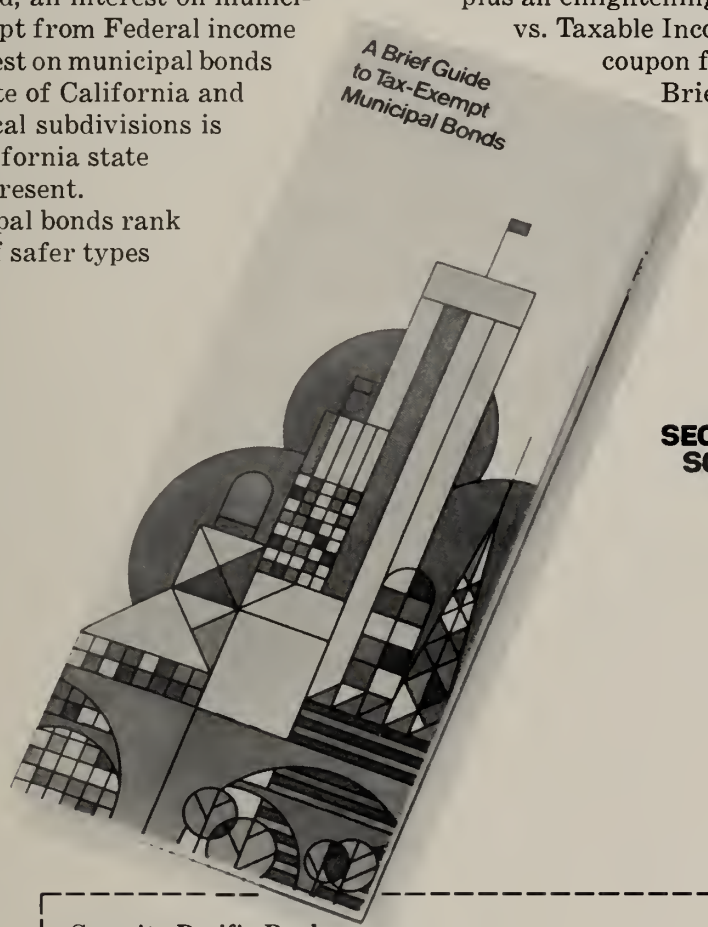

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Control of emesis has been shown to be equivalent to that achieved with Compazine® (prochlorperazine) and other potent phenothiazines in well-controlled clinical studies.*

Well tolerated

The parenteral solution is non-irritating and does not produce pain at the site of injection. Drowsiness appears to be the most common adverse reaction. Other more significant reactions have been reported: Please refer to the package insert.

Characteristically nonhypotensive

Emete-con™ (benzquinamide HCl) n be used in marginally hypotensive patier since it does not characteristically cause potentiate hypotension. Indeed, it has be reported to produce a pressor effect in some cases, and should therefore be use with caution in the debilitated, in hypertensives, and in patients with a history or current evidence of cardiovascular disease.

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Emete-con does not characteristical cause respiratory depression or potentia CNS depressants. On the contrary, it appears to counteract the respiratory depression which may be induced by th narcotics, morphine and meperidine, commonly used in the post-operative period.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Actions. Benzquinamide HCl has exhibited antiemetic, antihistaminic, mild anticholinergic and sedative action in animals. Studies conducted in dogs and human volunteers have demonstrated suppression of apomorphine-induced vomiting; however, relevance to clinical efficacy has not been established. The mechanism of action in humans is unknown. Onset of antiemetic activity in humans usually occurs within 15 minutes.

Benzquinamide metabolism has been studied in animals and in man. In both species, 5-10% of an administered dose is excreted unchanged in the urine. The remaining drug undergoes metabolic transformation in the liver by at least three pathways to a spectrum of metabolites which are excreted in the urine and in the bile, from which the more polar metabolites are not reabsorbed but are excreted in the feces. The half-life in plasma of Emete-con is about 40 minutes. More than 95% of an administered dose was excreted within 72 hours in animal studies using ^{14}C-labeled benzquinamide. In blood, benzquinamide is about 58% bound to plasma protein.

Indications. Prevention and treatment of nausea and vomiting associated with anesthesia and surgery.

The prophylactic use should be restricted to those patients in whom emesis would endanger the results of surgery or result in harm to the patient.

Contraindications. Contraindicated in individuals who have demonstrated hypersensitivity to the drug.

Warnings. *Use in Pregnancy:* No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children: As the data available at present are insufficient to establish proper dosage in children, use in children is not recommended.

Intravenous use: Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route should be restricted to patients without cardiovascular disease and receiving no pre-anesthetic cardiovascular and/or concomitant cardiovascular drugs.

Precautions. Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

Adverse Reactions. Drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected– *Autonomic Nervous System:* Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.

Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.

Gastrointestinal System: Anorexia, nausea.

Musculoskeletal System: Twitching, shaking tremors, weakness.

Skin: Hives rash.

Other Systems: Fatigue, chills, increased temperature.

Dosage and Administration. *Intramuscular:* 50 mg (0.5 mg/kg–1.0 mg/kg)

First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-con should be injected well within the mass of a larger muscle. The deltoid area should be used only if well developed. Injections should not be made into the lower and mid-thirds of the upper arm. Aspiration of the syringe should be carried out to avoid inadvertent intravascular injection.

Therapeutic blood levels and demonstrable antiemetic activity appear within fifteen minutes of intramuscular administration. When the objective of therapy is the prevention of nausea and vomiting, intramuscular administration is recommended at least fifteen minutes prior to emergence from anesthesia.

Intravenous: 25 mg (0.2 mg/kg–0.4 mg/kg as a single dose) administered slowly (1 ml per 0.5 to 1 minute). Subsequent doses should be given intramuscularly.

The intravenous route of administration should be restricted to patients without cardiovascular disease (See WARNINGS). If it is necessary to use Emete-con intravenously in elderly or debilitated patients, benzquinamide should be administered cautiously and the lower dose range is recommended. This preparation must be initially reconstituted with 2.2 ml of sterile water. This procedure yields 2 ml of a solution equivalent to 25 mg benzquinamide/ml, which maintains its potency for 14 days at room temperature. DO NOT REFRIGERATE.

Overdosage. *Manifestations:* On the basis of acute animal toxicology studies, gross Emete-con overdosage in humans might be expected to manifest itself as a combination of Central Nervous System stimulant and depressant effects. This speculation is derived from experimental studies in which intravenous doses of benzquinamide, at least 150 times the human therapeutic dose, were administered to dogs.

Treatment: There is no specific antidote for Emete-con overdosage. General supportive measures should be instituted, as indicated. Atropine may be helpful. Although there has been no direct experience with dialysis, it is not likely to be of value, since benzquinamide is extensively bound to plasma protein.

How Supplied. Emete-con for IM/IV use is available in a vial containing benzquinamide HCl equivalent to 50 mg of benzquinamide in packages of 10 vials.

***Bibliography**

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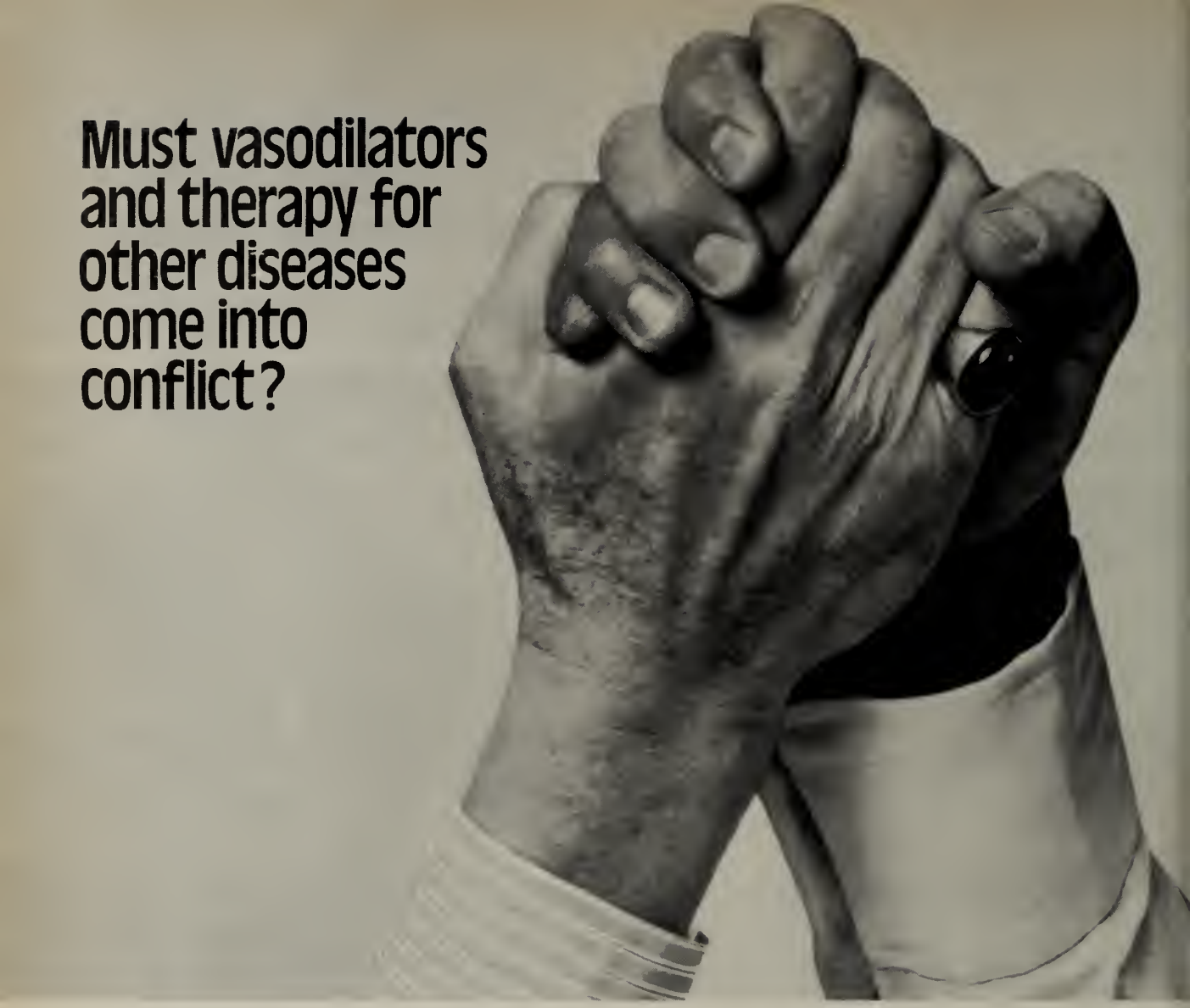
(benzquinamide HCl) IM/IV

post-op EMETIC-CONtrol

Usual adult dose: IM-50 mg., IV-25 mg.

Must vasodilators and therapy for other diseases come into conflict?



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The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

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Or a simple note on your prescription form will do.

Part of a series on the clinical, bacteriological and pharmacological aspects of Bactrim therapy.

This is Bactrim against E. coli, Proteus

These are results from clinical trials* in which patients with chroni urinary tract infections (primarily cystitis, pyelitis and pyelonephritis), more than half with obstructive complications, were treated with Bactri for 10 days and evaluated at intervals up to 32 days after termination of therapy. Patients were considered to have a significant bacteriologica response when the urine culture revealed 10,000 or fewer colonies/ml of any single organism cultured from a midstream clean-catch specime

Before prescribing Bactrim, please consult complete product informati for all adverse reactions, contraindications, precautions and warnings.

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performance
spp. and Klebsiella

	Excellent initial response* after 10 days of therapy	Impressive response maintained 32 days after termination of therapy
E. coli infections	97.1% of 105 patients	73.1% of 93 patients
Proteus spp. infections	81.1% of 37 patients	60.0% of 35 patients
Klebsiella infections	85.7% of 21 patients	65.0% of 20 patients

ta on file, Medical Department, Hoffmann-La Roche Inc., Nutley, New Jersey

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

In cystitis, pyelonephritis and pyelitis diagnosed as chronic and due to susceptible urinary tract pathogens, usually E. coli, Klebsiella-Enterobacter and Proteus mirabilis.

Please see following page for summary of product information.

In cases of cystitis, pyelonephritis and pyelitis diagnosed as chronic*

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

- aggressive antibacterial activity
- interrupts essential metabolic process of susceptible organisms, usually E. coli, Klebsiella-Enterobacter, P. mirabilis, and, less frequently, indole-positive proteus species
- over 91% initial efficacy in clinical studies of patients with urinary tract infection diagnosed as chronic*
- impressive response even in cases with obstructive complications
- not recommended for children under 12, during pregnancy or the nursing period
- no loading dose; two tablets b.i.d. recommended for 10-14 days

*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species).

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in chronic and recurrent urinary tract infections.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia in elderly patients on diuretics, primarily thiazides. Sore throat, fever, pallor or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. Data are insufficient to recommend use in infants and children under 12.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, allergy or bronchial asthma; and in those with glucose-6-phosphate dehydrogenase deficiency, where hemolysis may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: Two tablets b.i.d. for 10 to 14 days. For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	2 tablets every 24 hours
Below 15	Use not recommended

Supplied: Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10

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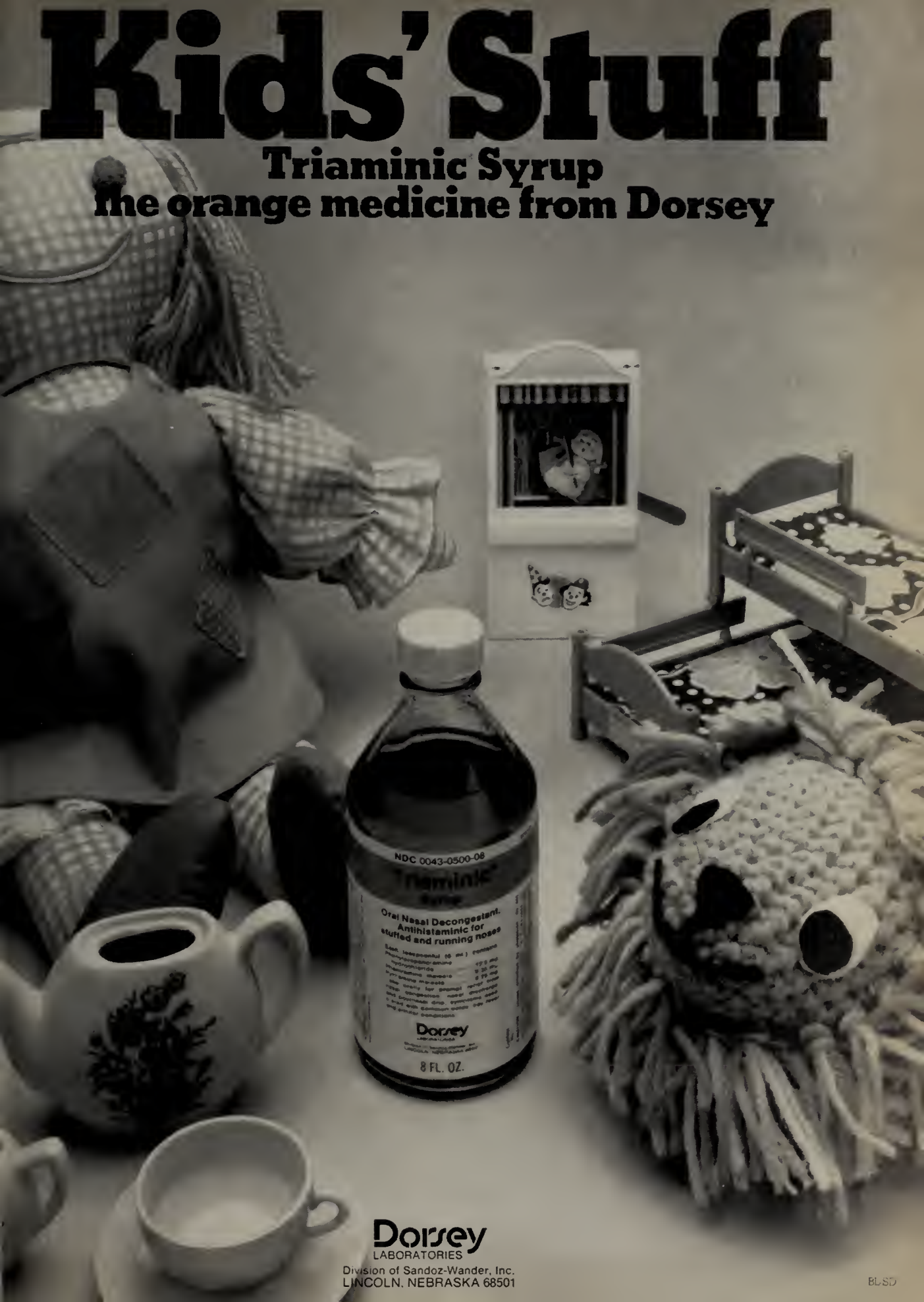

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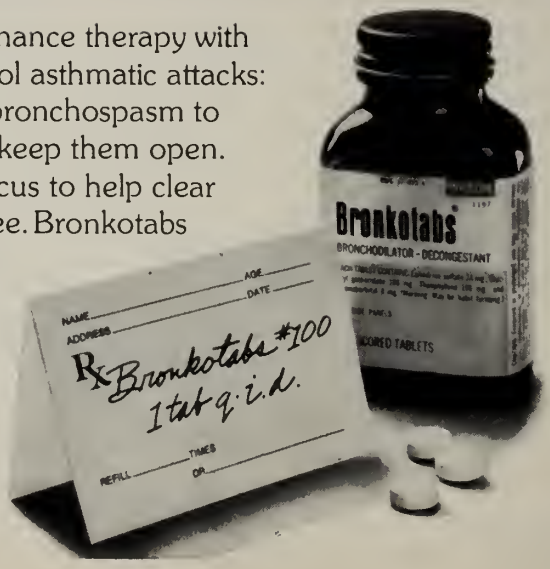

PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

DOSAGE: Adults, one tablet every three or four hours, four or five times daily. Children over six, one-half the adult dose. Children under six, as directed.

SUPPLIED: Bottles of 100 and 1,000 tablets.

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But they do know what meat is.

The foods above have several nutrients in common. They include cell-building protein, as well as niacin, iron and thiamin. Because of these common nutrients, these foods are considered a part of the Meat Group in the U.S. Department of Agriculture's Four Food Groups system.

Some physicians counsel patients in terms of nutrients. Which is easier for them to understand—foods or nutrients?

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The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

1 chance in 4 of solar keratoses*

At start of treatment with Efudex® (fluorouracil) Roche® 5% Cream—1/22/68. Patient shows widespread but mild solar keratoses.

Response after 11 days of treatment—2/2/68. Site of keratoses is now erythematous (erythematous reactions subside after therapy is discontinued). Lesions not visible before therapy have appeared. Intervening skin shows no response to application of cream.

One year after end of the —2/19/69. Skin appears clear, no evidence of sca ring. No recurrences or r lesions.

*Statistical projection based on an epidemiologic study of all white adults over 40 years of age in Tipton County, Tenn., to determine prevalence of solar keratoses.

People in southern areas of the United States are at more risk of eveloping solar keratoses than those in the northerly latitudes. But olar keratoses—also called actinic or senile keratoses—can occur mong any white-skinned population, wherever people work or play utdoors. And because lesions may be premalignant, it is generally greed that they should be treated. Conventional therapy may present ertain drawbacks for the physician as well as the patient, but Efudex luorouracil) Roche offers an alternative mode of therapy that's inxpensive, highly convenient, and almost always effective.

Selectivity of action

Healthy skin free of keratotic invasion shows no response to pplication of Efudex. Lesions which were not visible before therapy ppear during application. Since the response is so predictable, sions that do not respond should be biopsied to rule out the resence of frank neoplasm.

Excellent cosmetic results

Treatment with Efudex usually provides highly acceptable osmetic results, as is evident in the patient shown. The incidence scarring is low.† This is particularly important with multiple facial sions. Efudex should be applied with care near the nose, eyes nd mouth.

Convenience

To apply Efudex Cream to the skin, the patient may use a nonetal applicator, a suitable glove, or the fingertips. If the patient does ot wear a glove, the hands should be washed immediately after the edication is applied. Efudex Solution is supplied in a plastic disenser, which issues *only one drop* at a time—the Solution is very onvenient to use for treating single lesions. It's convenient for you, o, to prescribe Efudex 5% Cream because it's almost impossible r a pharmacist to compound a 5% fluorouracil cream that has not st its potency because of chemical degradation or evaporation ring compounding.

5% Cream—a Roche exclusive

Only Roche formulates the 5% cream—high in patient acceptaity—economical and superior in clinical efficacy to the 2% formuion for lesions of the hands and forearms.

ata on file, Hoffmann-La Roche Inc., Nutley, New Jersey.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Multiple actinic or solar keratoses.

Contraindications: Patients with known hypersensitivity to any of its components.

Warnings: If occlusive dressing used, may increase inflammatory reactions in adjacent normal skin. Avoid prolonged exposure to ultraviolet rays. Safe use in pregnancy not established.

Precautions: If applied with fingers, wash hands immediately. Apply with care near eyes, nose and mouth. Lesions failing to respond or recurring should be biopsied.

Adverse Reactions: Local—pain, pruritus, hyperpigmentation and burning at application site most frequent; also dermatitis, scarring, soreness and tenderness. Also reported—insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, lacrimation, leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.

Dosage and Administration: Apply sufficient quantity to cover lesion twice daily with nonmetal applicator or suitable glove. Usual duration of therapy is 2 to 4 weeks.

How Supplied: Solution, 10-ml drop dispensers—containing 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris (hydroxymethyl) aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Cream, 25-Gm tubes—containing 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Practical therapy—predictable response

Efudex® 5% Cream

fluorouracil/Roche®

for solar keratoses

Please send me a pad of the new Efudex® (fluorouracil) Roche® Patient Instruction Sheets. WJ

Dr. _____

_____
Street

_____
City State Zip

If we could have managed Mr. Hood's account, he'd be out of the woods.

Robin Hood handled a lot of money over the course of his career. But he found fortune easier to acquire than to retain. And spent most of his life living on nuts and berries.

He is not a lone example. Many talented, hard working people find it easier to make money than to manage it. Security Pacific Bank's Trust Department enables such people—and their families—to attain their economic goals. No single investor, no matter how sophisticated, could provide the time, research and collective experience that goes into the building of each portfolio.

Professional investment service is not the only benefit our trusts provide. Should you become ill or incapacitated, Security Pacific Bank will continue to manage your portfolio, and at the same time apply income to medical expenses and the needs of your family. Finally, a trust with Security Pacific Bank may enable you to combine tax savings, greater family income and even a gift to your favorite charity.

Mr. Hood would approve of that.

To make an appointment, call any of our over 470 branch offices. There is no cost or obligation.

SECURITY PACIFIC BANK
SOMETHING SPECIAL

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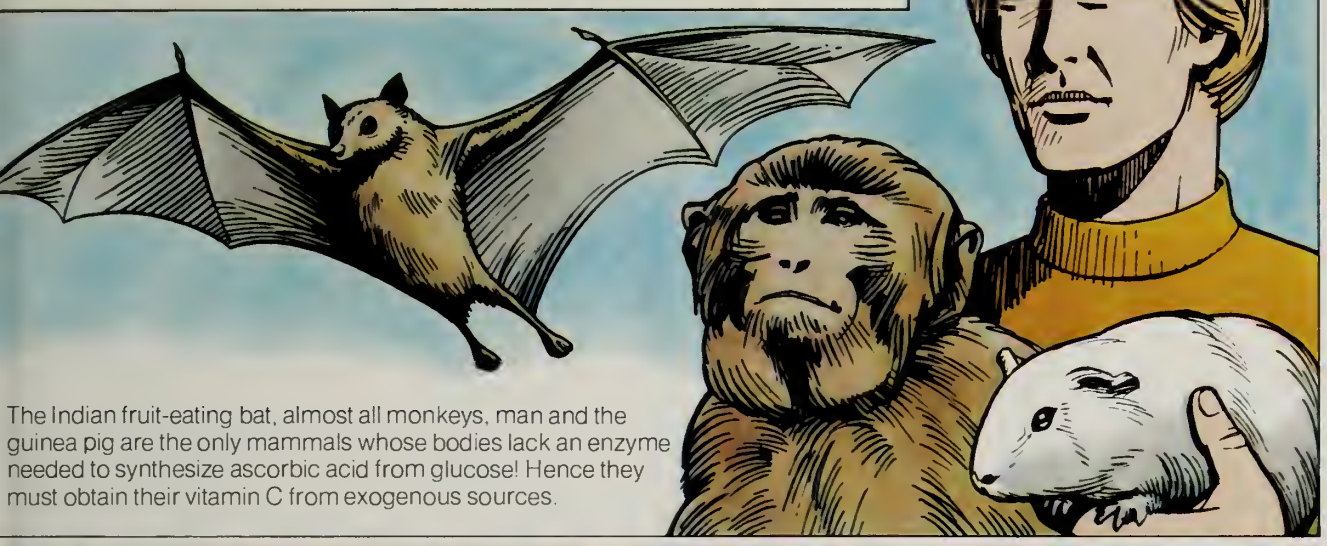
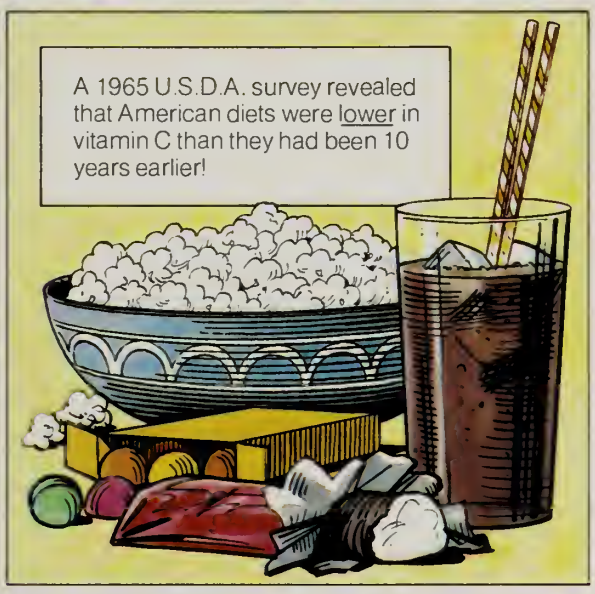
The ALLBEE® with C Scrapbook of Vitamin Facts & Fallacies



The Indian fruit-eating bat, almost all monkeys, man and the guinea pig are the only mammals whose bodies lack an enzyme needed to synthesize ascorbic acid from glucose! Hence they must obtain their vitamin C from exogenous sources.

De Joinville writing about a 13th century crusade reported that barber surgeons had to "cut away the dead flesh from the gums to enable people to masticate their food." The disease he described was probably scurvy.



The outer leaves of cabbage and brussels sprouts contain more vitamin C than the heads. Yet, ironically, these are often trimmed away by the grocer to improve appearance and enhance sales appeal! Many housewives trim them even more before cooking!

Available on your prescription or recommendation

ALLBEE® with C

High Potency B-Complex and Vitamin C Formula

A.H. Robins Company, Richmond, Va. 23220 A·H·ROBINS

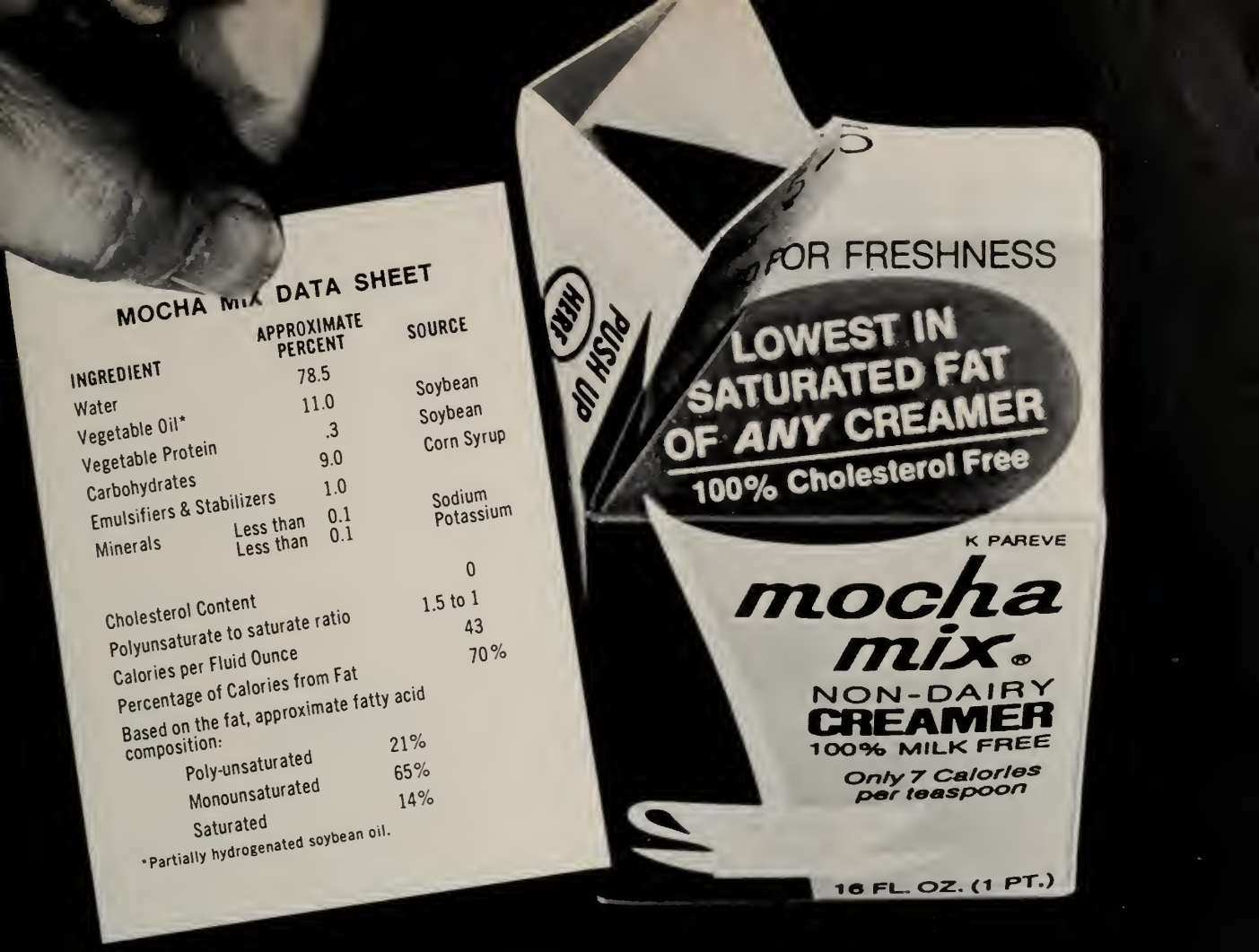
Spasm reactor?

Donnatal®!

	each tablet, capsule or 5 cc. teaspoonful of elixir (23% alcohol)	each Donnatal No. 2	each Extentab
hyoscyamine sulfate	0.1037 mg.	0.1037 mg.	0.3111 mg.
atropine sulfate	0.0194 mg.	0.0194 mg.	0.0582 mg.
hyoscine hydrobromide	0.0065 mg.	0.0065 mg.	0.0195 mg.
phenobarbital	(¼ gr.) 16.2 mg	(½ gr.) 32.4 mg.	(¾ gr.) 48.6 mg.
(warning: may be habit forming)			

Brief summary. Adverse Reactions: Blurring of vision, dry mou difficult urination, and flushing or dryness of the skin may occur higher dosage levels, rarely on usual dosage. Contraindicatio Glaucoma; renal or hepatic disease; obstructive uropathy (for ample, bladder neck obstruction due to prostatic hypertrophy) hypersensitivity to any of the ingredients.

A·H·ROBINS A H Robins Company. Richmond Virginia 232



Mocha Mix® presents its credentials:

Study them. Note how low Mocha Mix® is in saturated fat. (Actually the lowest of any creamer — liquid, frozen or powdered.) Then note the unsaturated to saturated fat ratio (1.5:1). And Mocha Mix is 100% milk-free and 100% cholesterol-free, too! Taste? In coffee . . . on cereal, fruit or desserts . . . or for cooking, any way, any time a creamer is called for, Mocha Mix is the most delicious creamer ever!

In addition to the 16 oz. size found in the dairy case of most grocery stores, Mocha Mix is available in larger sizes and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to: Mocha Mix Dept. Presto Food Products, Inc. P.O. Box No. 21908, Los Angeles, Calif. 90021

***mocha mix*. . . . the non-dairy creamer that's lowest in saturated fat!**

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

"...and she'd jump every time the phone rang."

"All right, I agree, she was obviously very anxious...you said she hadn't been sleeping..."

"She felt *tired enough* to sleep... not relaxed enough...food, too... she's too nervous to eat...says she *can't* relax...afraid there's something very wrong with her."

"...that's a good place to Did you find anything wr with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

MSD MERCK SHARP & DOHME

For a brief summary of prescribing information, please turn to the following page.

ot a thing... negative... nothing
ganically wrong. Still has a
ir list of somatic complaints.
e tried to reassure her... to let
r talk... to help her sort things
t. She's been in to see me a
mber of times."

"...what about medication?"

"Just what I was coming to...
I've had her on tranquilizers.
And *that's* what puzzles me. I'm
not getting the response I hoped
for. She's no better... perhaps a
little worse. It's sad to see."

"...I think *'sad'* may be what
you're not seeing! You know,
this sounds like another case
where the *anxiety* is so clear and
pervasive we tend to overlook
the depressive part of the picture.
I'm not sure that we shouldn't
almost always think of anxiety
with depression... not anxiety
alone. Take another look at your
records... talk to her some more.
If you decide she's depressed,
I think you might want to
consider TRIAVIL.... It can help
relieve her entire symptom
complex... control the anxiety...
while at the same time treat
the depression."

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

to help treat what you often find: obvious moderate to severe anxiety with a less obvious underlying depression

Available:
TRIAVIL® 2-25: Each tablet contains
2 mg. perphenazine and 25 mg. amitriptyline HCl

TRIAVIL® 2-10: Each tablet contains
2 mg. perphenazine and 10 mg. amitriptyline HCl

TRIAVIL® 4-25: Each tablet contains
4 mg. perphenazine and 25 mg. amitriptyline HCl

TRIAVIL® 4-10: Each tablet contains
4 mg. perphenazine and 10 mg. amitriptyline HCl

INITIAL THERAPY FOR MANY PATIENTS
TRIAVIL® 2-25 (or TRIAVIL® 4-25) t.i.d. or q.i.d.

FOR FLEXIBILITY IN ADJUSTING MAINTENANCE THERAPY
TRIAVIL® 2-10 (or TRIAVIL® 4-10)

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either constituent alone

Perphenazine: Side effects may be any of those reported wit phenothiazine drugs: extrapyramidal symptoms (opisthotonus, oc logyric crisis, hyperreflexia, dystonia, akathisia, acute dyskinesi ataxia, parkinsonism) can usually be controlled by the concomitan use of effective antiparkinsonian drugs and/or by reduction in do age, but sometimes persist after discontinuation of the phenothiazine

Tardive dyskinesia may appear in some patients on long-term the apy or may occur after drug therapy with phenothiazines and relate agents has been discontinued. The risk appears to be greater in derly patients on high-dose therapy, especially females. Symptom are persistent and in some patients appear to be irreversible. Th syndrome is characterized by rhythmical involuntary movements the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing cheeks, puckering of mouth, chewing movements). Involuntary mov ments of the extremities sometimes occur. There is no known tre ment for tardive dyskinesia; antiparkinsonism agents usually do n alleviate the symptoms. It is advised that all antipsychotic agents b discontinued if the above symptoms appear. If treatment is reinsti ted, or dosage of the particular drug increased, or another drug su stituted, the syndrome may be masked. It has been suggested th fine vermicular movements of the tongue may be an early sign of th syndrome, and that the full-blown syndrome may not develop if me cation is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itchin erythema, urticaria, eczema, up to exfoliative dermatitis); other lergic reactions (asthma, laryngeal edema, angioneurotic eder anaphylactoid reactions); peripheral edema; reversed epinephrin effect; hyperglycemia; endocrine disturbances (lactation, gala torrhea, gynecomastia, disturbances of menstrual cycle); altere cerebrospinal fluid proteins; paradoxical excitement, hypertensic hypotension, tachycardia, and ECG abnormalities (quinidine-like fect); reactivation of psychotic processes; catatonic-like states, a tonomic reactions, such as dry mouth or salivation, headach anorexia, nausea, vomiting, constipation, obstipation, urina frequency or incontinence, blurred vision, nasal congestion, and change in pulse rate; hypnotic effects; pigmentary retinopathy, c neal and lenticular pigmentation; occasional lassitude, muscle we ness, mild insomnia. Other adverse reactions reported with vario phenothiazine compounds include blood dyscrasias (pancytopen thrombocytopenic purpura, leukopenia, agranulocytosis, eosinop lia); liver damage (jaundice, biliary stasis); grand mal convulsior cerebral edema; polyphagia; photophobia; skin pigmentation; a failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported this drug, but which have occurred with other pharmacologically si lar tricyclic antidepressant drugs. *Cardiovascular:* Hypotension; pertension; tachycardia; palpitation; myocardial infarctio arrhythmias; heart block; stroke. *CNS and Neuromuscular.* C fusional states; disturbed concentration; disorientation; delusior hallucinations; excitement; anxiety; restlessness; insomnia; nig mares; numbness, tingling, and paresthesias of the extremitie peripheral neuropathy; incoordination; ataxia; tremors; seizures; al ation in EEG patterns; extrapyramidal symptoms; tinnitus. *A ticholinergic:* Dry mouth; blurred vision; disturbance accommodation; constipation; paralytic ileus; urinary retention; dila tion of urinary tract. *Allergic:* Skin rash; urticaria; photosensitizatic edema of face and tongue. *Hematologic:* Bone marrow depressi including agranulocytosis; leukopenia; eosinophilia; purpura; thro bocytopenia. *Gastrointestinal:* Nausea; epigastic distress; vomitir anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; bla tongue. *Endocrine:* Testicular swelling and gynecomastia in the ma breast enlargement and galactorrhea in the female; increased decreased libido; elevated or lowered blood sugar levels. *Other:* D ziness, weakness; fatigue; headache; weight gain or loss, increas perspiration; urinary frequency; mydriasis; drowsiness; jaundice, a pecia. *Withdrawal Symptoms:* Abrupt cessation after prolonged ministration may produce nausea, headache, and malaise. These a not indicative of addiction.

OVERDOSAGE: Treatment is symptomatic and supportive. Howev the intravenous administration of 1-3 mg of physostigmine salicyl has been reported to reverse the symptoms of amitriptyline pois ing. On this basis, in severe overdosage with perphenazine-a triptyline combinations, symptomatic treatment of cent anticholinergic effects with physostigmine salicylate should be c sidered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

MSD
MERC
SHARP
DOHM

Case history #6

Vernon's well-being comes first.

Vernon's being well comes first.

On October 26, 1963, Vernon Bailey was working atop an oil derrick in Bakersfield hen he lost his footing and fell 35 feet to the ground, suffering a spinal injury with permanent paraplegia. The hardest years of his life began.

State Compensation Insurance Fund helped the primary physician to transfer Vernon nmediately to a Spinal Cord Center, where he was taught the necessary medical techiques and skills of self-care that would enable him to live as full and normal a life as ossible.

For the next ten years, State Fund's rehabilitation team worked closely with Vernon nd his doctors in helping to rebuild his life.

Today, although Vernon has been unable to return to work, his financial future is ecure. Arrangements were made for Vernon to receive a lump-sum payment of his projected fetime benefits, and State Fund helped him invest the money wisely.

Vernon has come a long way since 1963. His problems aren't over, but he has built imself a future—with the help of State Fund.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND

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PHYSICIANS WANTED

PSYCHIATRISTS, GP'S for geriatric program within State hospital 50 miles north of Los Angeles. Fine climate near beaches. Salary $23,484 to $31,488. Optional monthly OD 5% extra. Other fringe benefits. Contact: Martin Gish, MD, Program Director (6G), Box A, Camarillo, CA 93010. Telephone (805) 482-4671, ext. 2638.

CARDIOLOGIST—Board certified internist with subspecialty in cardiology needed for busy cardiology practice in Orange County, with excellent facilities and adjacent medical school. Send résumé to Box 9392, Western Journal of Medicine, 731 Market St., San Francisco, 94103.

FULL-TIME EMERGENCY CARE position with pre-payment group. Includes both hospital and clinic emergency care work. Partnership after two years. Excellent insurance and retirement programs. Robert A. McFarlane, MD, 5055 North Greeley Ave., Portland, Ore. 97217.

SEMI-RETIRED or other for light pleasant duties, average six hours daily, in medium size Central California community. Salary negotiable, many fringe benefits. Send curriculum vitae to P.O. Box 215016, Sacramento, CA 95821 or call (916) 927-8126.

CLINIC PHYSICIAN IN HEALTH DEPARTMENT . . . Immediate vacancy physician who possesses California license needed to conduct out-patient clinics, participate in child health conferences, family planning, communicable disease and immunization clinics. Competitive salary and top fringe benefits. Contact O. A. Kearns, MD, Health Officer, Kern County Health Department, P. O. Box 997, Bakersfield, California 93302, or call (805) 861-3655.

PSYCHIATRIST AND GENERAL PHYSICIANS—Immediate employment in modern mental hospital fifty miles north of Los Angeles. Pleasant surroundings. New salary schedule effective July 1, 1974, commencing at $35,736 per year. Contact Robert E. Moebius, MD, Chief of Professional Education, Camarillo State Hospital, Box A, Camarillo, CA 93010. Phone: (805) 482-4671, extension 2893.

BOARD CERTIFIED RADIOLOGIST, well experienced in diagnosis, including angiography and isotopes. now on staff of large well known private hospital, as well as on clinical faculty of University, wishes to relocate. Interested in hospital or group practice, WILLING TO INVEST. Box 9382, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

APRICOT CAPITAL OF THE WORLD seeks sixth family physician. Guaranteed salary or office sharing available. On-call every fifth night. Accredited 45-bed hospital in town. Peter La Torre, MD, 101 No. 3rd St., Patterson, CA 95363.

PHYSICIAN-ADMINISTRATOR for a growing community clinic in So. Cal. town of about 60,000. Serves medically indigent and those unable to find medical care, about 40 percent Spanish speaking. $22,000-$26,000. Contact Escondido Community Clinic, 401 N. Spruce, Escondido, CA 92025, (714) 747-6610.

PHYSICIANS WANTED

ENJOY THE GOOD LIFE . . . along with an attractive salary and outstanding benefits. Join an expanding group practice HMO in Southern California beach communities. More than 10 years of HMO practice. Selected openings in all specialties. Inquire today. Frank Volpe, MD, Medical Director, Family Health Program, Room 9419, 2925 N. Palo Verde Ave., Long Beach, CA 90815.

INTERNIST who desires 3-day week, adequate income, near Monterey Peninsula, golf, sailing, beach walking, whatever. No night, hospital work. Share large practice, functional office, modest overhead, no partnership obligations. Ideal for man wanting some work, much leisure. Interested? Write: Box 9396, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

IDEAL SAN FRANCISCO BAY AREA LOCATION—Position for Chief, Preventive Medical Services; responsible for Tuberculosis Control, Maternal and Child Health, Dental Health and Communicable Diseases; will serve as Chief, Deputy Health Officer, three years clinical and medical administrative experience and valid California Medical License, MPH desirable but not required. Salary $27,264 to $33,132 based on experience. Immediately available. For further information contact Alameda County Health Care Services Agency—Public Health Service, Morton Nelson, MD, 499 - 5th St., Oakland, CA 94607.

ALAMEDA COUNTY HEALTH CARE SERVICES AGENCY—Position for Chief, Bureau of Communicable Disease; responsibilities include Tuberculosis Control, Venereal Disease and Immunization; serves as professional consultant to private and public medical sector. Combination of clinical and medical administrative experience desirable. Valid California Medical License. MPH desirable but not required. Salary $27,264 to $33,132 based on experience. Available September 1, 1974. For further information contact Alameda County Health Care Services Agency, Morton Nelson, MD, 499 - 5th St., Oakland, CA 94607.

CHIEF, OFFICE OF MEDICAL CARE — Background in public health and preventive medicine; responsibilities include assessment of Agency's medical care, primary care and preventive medicine; to establish, coordinate and monitor health standards in the Agency's jurisdiction. Valid California medical license. MPH desirable but not required. Salary $27,264 to $33,132 based on experience. Available July 1, 1974. For further information contact Alameda County Health Care Services Agency—Public Health Service, Morton Nelson, MD, 499 - 5th St., Oakland, CA 94607.

MEDICAL DIRECTOR—Santa Barbara County has opening in 50-bed hospital in Santa Maria. Will have charge of medical services and the development of care and treatment programs. Valid California license to practice medicine and two years of administrative experience in a general hospital. $30,393-$37,103. Apply Personnel Dept., 123 E. Anapamu St., Santa Barbara, CA 93101.

DEPUTY HEALTH OFFICER — Santa Barbara County has opening in Santa Maria area for person to direct the child health and disability prevention program as well as providing professional medical services in a public health program. Cal. license to practice medicine and three years clinical experience in a public health program including one year in administering health services for children. $28,202-$34,429. Apply Personnel Dept., 123 E. Anapamu St., Santa Barbara, CA 93101.

MEDICAL PRACTICE OPPORTUNITIES for family practitioners, pediatricians, internists, and OB-Gyn available in Antelope Valley, only one freeway hour from metro-Los Angeles. Desirable, uncrowded area; no smog or traffic worries. Modern medical center with new wing currently under construction. Contact: Lee E. Bockhacker, MD, Antelope Valley Hospital Medical Center, 1600 West Ave. "J", Lancaster, CA, (805) 948-4577.

(Continued on Page 30)

- ER
- GEN. PRACTITIONERS
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Tremendous opportunities to those with California license. Rapidly growing medical group—hospital affiliated. Long Beach & other So. Calif. areas.

TOP SALARY
plus fringe benefits
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Needed for part-time and full-time employment with Los Angeles County Dept. of Personnel Occupational Health Service. Openings are in pre-employment medical examination and employee health programs. Salary commensurate with training and experience.

For further information please contact Gary Fowler, Administrative Director, Occupational Health Service, Dept. of Personnel, Room B-50, Hall of Administration, 222 N. Grand Ave., Los Angeles, CA 90012. (213) 974-2658.

SANTA BARBARA, California desires **DIRECTOR OF MEDICAL EDUCATION** for accredited program—Internist or Family Practitioner. Contact: Larry F. Smith, MD, Chairman of the Education Committee, P.O. Box 689, Santa Barbara, CA 93102.

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ALLERGENIC EXTRACTS

- *specialized allergy service*
- *diagnostic and therapeutic extracts*

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PERSONAL SERVICE

Frees you from details and delays.
Provides you with ready-to-use extracts.
Descriptive literature sent on request.

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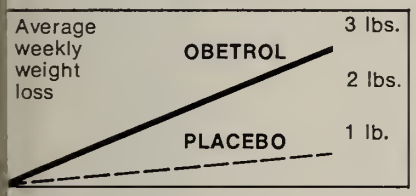
EFFECTIVE APPETITE DEPRESSANT with predictable pharmacological action

OBETROL® CII

Single entity amphetamine product. Each OBETROL-10 (10 mg. tablet) contains: dextroamphetamine saccharate 2.5 mg., amphetamine aspartate 2.5 mg., dextroamphetamine sulfate 2.5 mg., amphetamine sulfate 2.5 mg. OBETROL-20 (20 mg. tablets) contain twice this potency.

Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

CONTROLLED STUDY —
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
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Superinfections of the Lung

An Evaluation by Serial Transtracheal Aspirations

E. JACK BENNER, MD, JURG P. MUNZINGER, MD, *and* RICHARD CHAN, MD, *Sacramento*

A prospective evaluation of cephaloridine, cephalothin, and lincomycin was conducted in 85 patients with pneumonia. None of the 50 with previous history of allergic sensitivity to penicillin had an allergic reaction. All cases of pure "pneumococcal pneumonia" were cured, regardless of the drug. Eight patients with polymicrobial pneumonia were cured by the cephalosporins, while lincomycin was ineffective in four patients who had polymicrobial pneumonia.

Although expectorated sputum and exudates from the nasopharyngeal and oropharyngeal areas contained large concentrations of Staphylococcus aureus and various Gram-negative bacillary species during and at the end of therapy, serial cultures of transtracheal aspirate and the clinical course failed to confirm "superinfection" of the lung.

THE USE OF ANTIBIOTICS for therapy of infections (or non-infections) in this country has been called "human carnage,"[1] and wrong and unnecessary in as many as 51.5 percent of patients.[2] It has been stated that "a well trained actor" could prescribe as wisely as physicians.[3] These accusations give rise to a question as to why antimicrobial therapy may appear unnecessary or incorrect when reviewed by some clinical investigators. One field in which this problem can be analyzed is that of antimicrobial therapy of pneumonia, where the accusation has been made that "superinfection" has been a common sequel of antimicrobial therapy.[4]

A recent study of patients suspected of having putrid anaerobic pulmonary infections clearly documented that appropriate diagnosis, including anaerobic pathogen recovery, could be accomplished quickly and accurately by percutaneous transtracheal aspiration, and that appropriate therapy led to cure of most infections.[5] Several studies have shown that recovery of bacteria from expectorated sputum does not usually reflect the types or numbers of pathogens present at the site of the infectious process in the lung.[6-8] To accurately evaluate the usefulness of expectorated sputum in making the initial diagnosis, and to observe the effect of antimicrobial therapy on changes of bacterial flora in expectorated sputum, in tracheal aspirate material, and in "superinfection," a quantitative prospective study was carried out. Changes in bacterial flora of expectorated sputum were

From the Department of Medicine, University of California, Davis, School of Medicine and The Sacramento Medical Center.

Dr. Chan was a Post-Doctoral Fellow in Infectious Diseases supported by NIH Training Grant No. 1T01 A1 0038-02 from the National Institute of Allergy and Infectious Diseases.

Submitted April 10, 1974.

This study was supported in part by a Grant-in-Aid from the Upjohn Company, Kalamazoo, Michigan.

Reprint requests to E. J. Benner, MD, No. 1 Scripps Drive, Suite 203, Sacramento, CA 95828.

compared to changes in the flora obtained by percutaneous transtracheal aspiration (TTA). The antimicrobial agents chosen for evaluation were cephaloridine or cephalothin versus lincomycin, because: (1) They are used as alternatives for penicillin in therapy of pneumonia, (2) they are effective for *in vitro* killing of Diplococcus pneumoniae, and (3) the antibacterial spectrum of the cephalosporins is quite different from lincomycin. The results in 85 patients treated for pneumonia at the Sacramento Medical Center are presented.

Methods and Materials

All patients included in the study had a working diagnosis of "pneumococcal pneumonia" based on a history suggesting acute infection of the lung, the physical signs of an inflammatory consolidation of lung(s), radiographic evidence consistent with pneumonitis, an elevated leukocyte count, fever, and Gram stain of expectorated sputum with a predominance of Gram-positive diplococci and pus cells. The mean age of the group was 61.5 years (range 28 to 89), and the symptoms were present from 24 to 96 hours before admission (mean 51 hours).

Therapy with lincomycin (Lincocin®) or cephaloridine (Loridine®) was decided in a randomized order, with 35 patients treated with each drug. Cephalothin (Keflin®) was used for 15 patients because of the personal wishes of the specific responsible physician, and these patients are included for completeness. Fifty of the patients were selected for the study because of a history of maculopapular rash or urticaria following previous therapy with penicillin. Of these 50 patients, 19 received cephaloridine, 8 received cephalothin and 23 received lincomycin.

Cephalothin was administered intravenously in doses from 6 to 8 grams daily. Lincomycin, in a dosage of 25 mg per kg of body weight per 8 hours (1.5 to 2.5 grams per dose), was given intravenously, and cephaloridine in doses of 35 to 50 mg per kg per 6 hours (not exceeding 4 grams daily) was given intramuscularly. When the decision was made to include the patient as a part of the study, surveillance for superinfection and toxicity was started. This consisted of quantitative cultures of expectorated sputum, nasopharyngeal exudate, oropharyngeal exudate and material obtained from the depths of the airways by percutaneous transtracheal aspiration. These specimens were collected just before therapy was begun, then again on days 3 to 5 of therapy, and again on the last day of therapy, or the next day.

Nasopharyngeal and oropharyngeal specimens were collected on a calcium alginate swab. The swab and its exudates were dissolved in 1 ml of a buffered diluent by mixing in a vortex for 2 to 3 minutes. This was diluted serially and inoculated on plates as undiluted, 10^{-2}, 10^{-4}, and 10^{-6} dilutions. Results were reported as numbers of colony-forming units per swab, which usually held 0.1 ml of exudate (as determined by weighing of several samples). Sputum was homogenized by mixing in a vortex in phosphate buffered saline solution, then was diluted to 10^{-3}, 10^{-5}, and 10^{-7} and inoculated. Transtracheal aspirate was processed in the same way, but an undiluted specimen was also cultured. All dilutions of all specimens were inoculated on a sheep blood agar plate containing 0.3 percent yeast extract, a peptic digest agar plate, a MacConkey agar plate and a colistin-nalidixic acid Columbia base blood agar plate. The plates were incubated in flowing 5 percent CO_2 for 24 hours, then quantitative counts determined. Standard bacteriologic methods were used for bacterial identification.

Results

Correct interpretation of the data requires recalling that each patient was believed to have pneumococcal pneumonitis. The results of microscopic examination of initial expectorated sputum for all 85 patients were "predominantly Gram-positive diploccoci" with many pus cells. Although the smear of expectorated sputum yielded recovery of D. pneumoniae in only 73 of the 85 patients despite inoculation and incubation within 30 to 60 minutes of collection, culturing of transtracheal aspirate allowed recovery of D. pneumoniae (more than 10^5 organisms per ml of aspirate) in all 85 cases. Thus, expectorated sputum culture was inadequate in 12 of the 85 patients. Furthermore, unsuspected pathogens (not seen on smear of expectorated sputum) were recovered in quantities of more than 10^7 bacteria per milliliter in transtracheal aspirate on the initial cultures from 11 patients. These were Haemophilus spp. in seven instances and Neisseria meningitidis in four instances. On initial examinations, therefore, transtracheal aspirate provided cultural confirmation of D. pneumoniae in 12 patients and yielded an important second pathogen in 11 patients where examination of expectorated sputum was misleading.

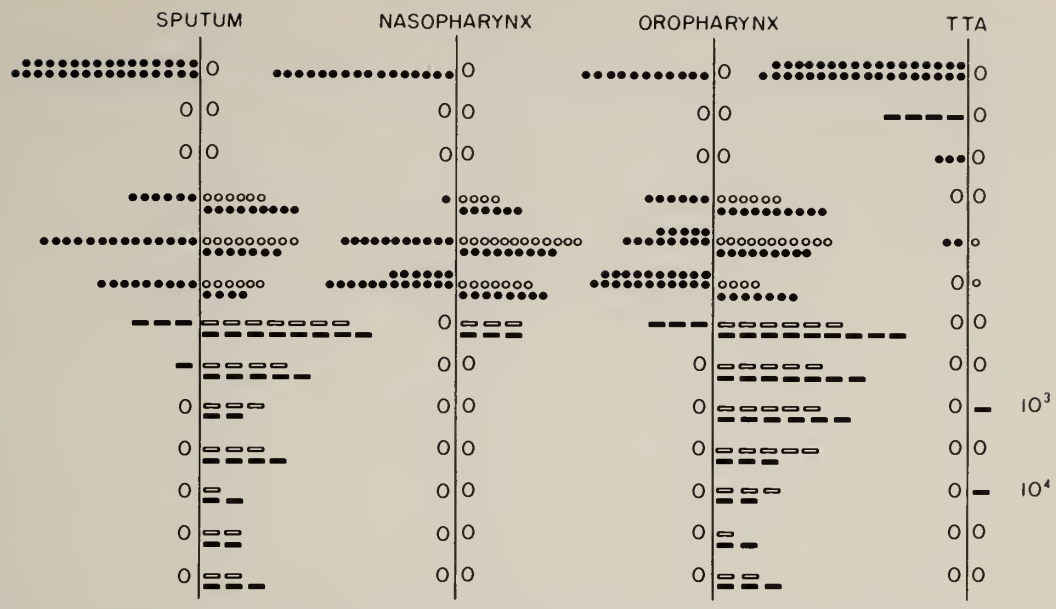

Chart 1.—Results of quantitative cultures in 35 patients treated with cephaloridine. Each closed circle or solid bar in the left columns represents a pre-therapy culture with more than 10^7 bacteria per ml. Each open circle or open bar in the right columns represents a culture with more than 10^7 bacteria per ml collected during therapy. Each closed circle or solid bar in the right columns represents a culture with more than 10^7 bacteria per ml (except when actual numbers are shown) collected at the conclusion of therapy.

Results with cephaloridine

In the 35 patients treated with cephaloridine, all had a clinical cure and none required a second course of an antimicrobial agent or a change in drug. In the six instances in which a second pathogen was recovered by TTA, the organisms (either N. meningitidis or Haemophilus spp.), as well as the pneumococcus, were eradicated. No allergic reactions occurred, although 19 patients gave a history of previous suspected hypersensitivity to penicillin. No other side effects or toxicity occurred.

However, the effect of this therapy on the microbiota of the respiratory system was dramatic (Chart 1). Expectorated sputum cultures obtained on days 3 to 5 of therapy showed that six patients harbored more than 10^7 S. aureus per ml of sputum. In addition, the large numbers of E. coli (seven cases), Klebsiella pneumoniae (four cases), Enterobacter aerogenes (three cases), Pseudomonas aeruginosa (three cases), Serratia marcescens (two cases), proteus (one case) and other Gram-negative bacilli (two cases) suggested frequent "superinfection." At the conclusion of therapy (Chart 1), more patients had large numbers of these pathogens in expectorated sputum. Although the nasopharynx contained similar pathogens during therapy, this was not as common a site for their recovery as was the oropharynx.

Despite the presence of large numbers of several strains of pathogenic bacteria from the upper respiratory system in these patients, pathogens were recovered from the lower respiratory system by TTA in only 2 of the 35 patients. One patient had E. aerogenes (10^3 per ml of TTA) and one had Proteus rettgeri (10^4 per ml). Both remained well without additional therapy during the six-week follow-up period.

Results with Lincomycin

There were 31 patients treated with lincomycin who had good clinical response with rapid eradication of infection. Three patients who had more than 10^7 per ml hemophilus organisms in the initial TTA, and one with this number of N. meningitidis in the TTA had persistence of these pathogens and a worsening of their clinical condition despite 48 hours of lincomycin therapy. They required a different antibiotic to effect a cure of their pneumonias.

Five of the 31 patients cured of their pneumonia had significant numbers of bacteria in the TTA taken at the end of therapy (Chart 2). The presence of large numbers of staphylococci, pseudomonads, and other Gram-negative bacillary species in expectorated sputum, the oropharynx, and to a lesser extent the nasopharynx (Chart 2), shows that lincomycin was as effective in changing the

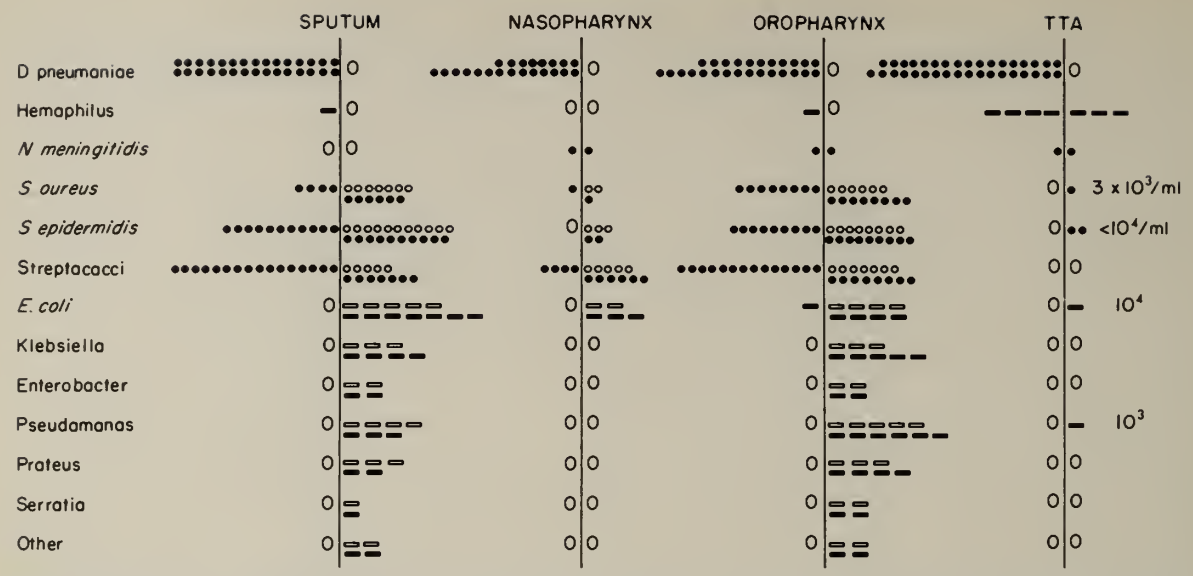

Chart 2.—Results of quantitative cultures in 35 patients treated with lincomycin. Specimen symbols are the same as in Chart 1.

microbiota of the upper respiratory system as cephaloridine. These changes in the upper airway bacterial populations did not reflect changes in the lower airways, however, since TTA was free of bacteria in 26 of the 31 cases. As with patients who were treated with cephaloridine, the five patients in this group who had 10^3 to 10^4 bacteria per ml of TTA at the end of therapy, remained clinically well during the six-week follow-up period.

Results with cephalothin

The 15 patients who received cephalothin had a similar change in the microbiota of the expectorated sputum, oropharynx and nasopharynx (Chart 3). Two patients had small numbers of Gram-negative bacilli recovered from TTA material obtained at the end of the therapy period, but they also remained well without further therapy.

Patients with pathogens in TTA material at the end of the therapy period

There were 11 patients in the total of 85 who required mechanical respiratory assistance and frequent, energetic tracheal suctioning. Of these, 10 were mentally obtunded for 24 to 72 hours after admission. Within this group of 11 patients, were the 8 who had pathogens in the TTA material obtained at the end of the therapy period. The organisms were S. aureus in two cases and E. coli, K. pneumoniae, E. aerogenes, P. rettgeri, S. marcescens, and P. aeruginosa in one case each. Since all of these patients had large numbers of these bacteria in the oropharynx and nasopharynx when cultures were taken on days 3 to 5, it is probable that these were aspirated or mechanically transmitted into the lower airway.

Complications

In the group of 85 patients, all had at least two TTA procedures. A total of 231 such procedures were done. All were done by or under the direct supervision of an experienced person. There were 17 episodes of minor subcutaneous emphysema and two of subcutaneous and intrathoracic emphysema. None of these caused morbidity or required therapy. There were 22 episodes of minor hemoptysis for a few hours after the procedures. All stopped spontaneously and were considered insignificant.

Discussion

These prospective data confirm that lincomycin, cephaloridine and cephalothin were all effective in eradicating D. pneumoniae from patients with pneumonitis and can, therefore, be used as safe, efficacious alternatives to benzylpenicillin for treating pneumococcal pneumonia. There were no hypersensitivity or toxicity reactions in this group of patients treated with reasonable doses based on body weight.

However, it was documented that all three drugs caused a dramatic change in the bacterial

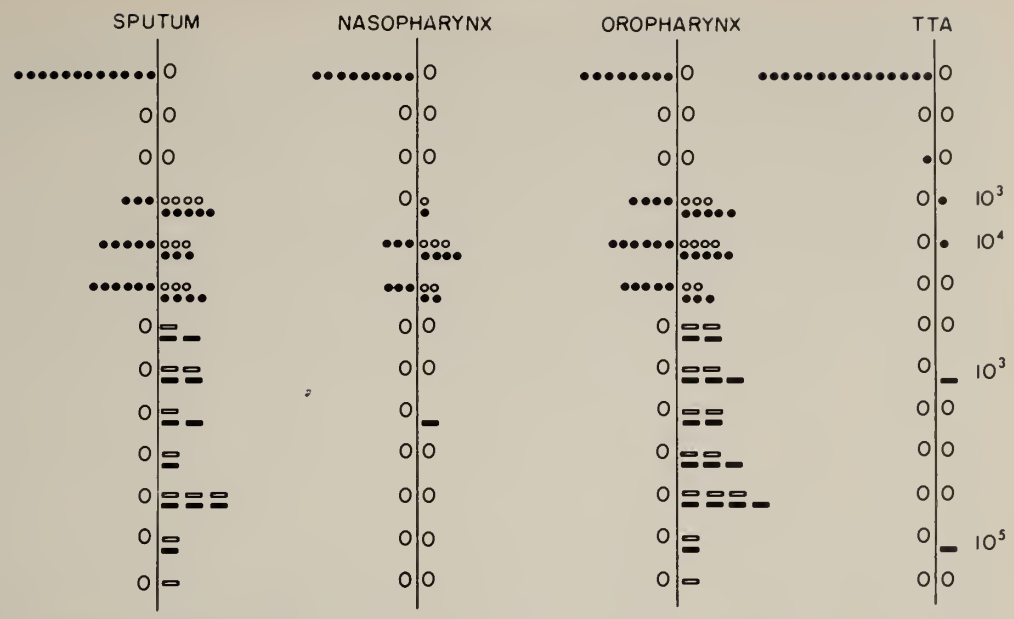

Chart 3.—Results of quantitative cultures in 15 patients treated with cephalothin. Specimen symbols are the same as in Chart 1.

populations of the upper airway. Staphylococcus aureus and Gram-negative bacilli occurred in large numbers (more than 10^7 per ml) in expectorated sputum, nasopharyngeal and oropharyngeal exudates in 52 percent of the specimens taken during and at the end of therapy. On the other hand, only in eight patients who had mental obtundation, repeated tracheal suctioning, and mechanical ventilatory assistance, did these pathogens occur in the depths of the airway when sampled by TTA. Although these eight patients had at least one of the potential pathogens present in TTA material at the end of their therapy, cessation of antimicrobial therapy was associated with clinical and radiologic evidence of cure of pneumonitis and they remained well during a six-week follow-up period.

The opinion that hospital-acquired respiratory infections make up 15 to 35 percent of reported nosocomial infections (a prevalence of 0.5 to 5.0 per 100 hospital admissions) was derived from data developed by culturing expectorated sputum.[9] Our data would suggest that this incidence may be grossly exaggerated as an indication of infection of the tracheobronchial tree or lung tissue.

The suppression of normal pharyngeal flora and emergence of staphylococci and a Gram-negative flora by antibiotic therapy has frequently been observed.[4,10] Although the ultrasonic type of nebulizer and mechanical ventilating equipment have occasionally been recognized as responsible for a specific outbreak of nosocomial infections,[9] there is no documentation that such infections are common unless the equipment is grossly contaminated.

Likewise, pharyngeal bacteria frequently enter the tracheobronchial tree as a consequence of intubation.[11] Since the eight patients who had contamination of their lower airway also were obtunded, required repeated tracheal intubation for suctioning and had mechanical ventilatory assistance, it is not hard to appreciate the mechanism of lower respiratory tract colonization by pharyngeal bacterial residents. It is evident that antibiotic therapy did not cause superinfections in the lungs. Instead, antibiotics changed the pharyngeal flora. If a patient is obtunded and aspirates large numbers of these new inhabitants, usually staphylococci or Gram-negative bacilli or both, or if repeated tracheal suctioning or mechanical ventilation forces these pathogens into the depths of the lung, infection can occur. It was apparent that infection of the lung did not necessarily occur when this sequence of events happened, since the eight patients recovered without antibiotic therapy. It is likely that factors of host resistance such as loss of mucociliary function[12,13] or impairment of function of the alveolar macrophages, which normally clear bacteria from the lung,[14] may need to be damaged before true superinfection develops.

The role of the physician in preventing "superinfections" of the lung should, therefore, be to minimize contamination of the lower airways by avoid-

ing unnecessary suctioning or ventilator assistance; to prevent introduction of bacteria from ventilatory or suction equipment; and to improve host resistance factors as much as possible by promoting consciousness and correcting metabolic derangements. However, most importantly, the physician must not change antibiotic therapy, or stop antibiotic therapy just because a culture of expectorated sputum contains staphylococci or Gram-negative bacilli. An accurate estimate of the bacteria present in the depths of the airways can and should be obtained by TTA cultures.[15] Serious complications have occurred,[16] but not when the precautions outlined by Kalinske et al[6] were carefully adhered to. TTA frequently provided valuable diagnostic information that prevented unnecessary change of, or addition of, other antimicrobial agents in a large number of the patients. Reliable diagnostic efforts in patients believed to have "putrid anaerobic infections"[5] or classic "pneumococcal pneumonia" seem to be the key to prompt, effective therapeutic measures. Likewise, during therapy, recovery of a potpourri of pathogens from sputum should prompt reliable specimen collection rather than addition of or change of antimicrobial regimen. Cooperation between clinician and the laboratory is imperative here. It must be borne in mind that the routine culturing of expectorated sputum collected while a patient is receiving antimicrobic agents, with recovery of the potpourri of pathogens, then extensive susceptibility testing and the reporting of these data can lead to misinterpretation of true data and to therapy that might lend credence to the damning charges referred to in the first paragraph of this communication.

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Refer to: Hattersley PG, Engels JL: Neutrophilic hypersegmentation without macrocytic anemia. West J Med 121:179-184, Sep 1974

Neutrophilic Hypersegmentation Without Macrocytic Anemia

PAUL G. HATTERSLEY, MD, *and* JUDITH L. ENGELS, MT, *Sacramento*

In five months of examining some 25,000 blood smears of hospital and clinic patients, 200 patients were found whose blood had hypersegmented neutrophiles without macrocytosis of the erythrocytes. Sixty-five of these patients subsequently received adequate laboratory work-up. Seven proved to have a bacterial inhibitor in their serum which interfered with the microbiological assay of folic acid. Of these patients, six had normal B-12 levels. Of the remaining 58, 45 had a deficiency of folate, of vitamin B-12 or of both. In 13, no such deficiency could be established. Of these, seven proved to be uremic. It is concluded that the additional effort required to search carefully for hypersegmentation, even in the absence of erythroid macrocytosis, is thoroughly justified, and that a large percentage of those patients in whose blood hypersegmented neutrophiles are found will prove to have important deficiencies of folate or B-12, or will prove to be uremic.

HYPERSEGMENTATION OF THE NEUTROPHILES and macrocytic anemia traditionally go hand in hand in patients with chronic folate or vitamin B-12 deficiencies. Herbert,[1] during the course of producing experimental folate deficiency in a well-nourished volunteer, showed that the first hematologic abnormality to appear was neutrophilic hypersegmentation. This occurred long before the appearance of macrocytic anemia, presumably because of the greater life span of normal erythrocytes, as compared with the brief intra-vascular life of the neutrophiles. More recently,[2-4] hypersegmented neutrophiles have been noted in the blood of patients with the uremic syndrome, but without macrocytic anemia, and in some cases with only borderline deficiency of folate. In addition, patients receiving certain cytotoxic drugs may show megaloblastic changes in the face of normal folate and B-12 levels.

It would appear, therefore, that a diagnosis of early or acute folate and B-12 deficiency will be overlooked if macrocytosis and anemia are considered requirements for such a diagnosis. To detect such deficiencies, one should also look for hypersegmented neutrophiles in the blood of persons without macrocytic anemia.

Working on this thesis, and as part of our continuing emphasis on the importance of careful

From the Departments of Internal Medicine and Clinical Pathology, University of California, Davis, School of Medicine, and Sacramento Medical Center.

Submitted, revised, February 11, 1974

Reprint requests to: P. G. Hattersley, MD, Sacramento Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817.

morphologic study,[5] we have searched for hypersegmented neutrophiles in all of the blood smears processed in our hematology laboratories. All smears thought by staff technicians to show signs of hypersegmentation have been examined by at least two additional trained observers. Particularly prominent in our series have been blood specimens showing absolute neutrophilic leukocytosis and toxic granulation without an increase in nonsegmented or "banded" neutrophiles. When we encountered hypersegmentation in the absence of macrocytosis, we sent to the clinical record a note describing our findings, and suggesting further study including serum folate and B-12 tests, and possibly a bone marrow examination.

In a period of about five months, during which technicians examined approximately 25,000 blood smears, we found 200 patients whose blood showed hypersegmentation without macrocytosis of the erythrocytes. This report summarizes our findings, and includes several characteristic case histories.

Methods*

All blood counts were done on the Coulter Counter Model S, which we have standardized against the cyanmethemoglobin technique, the microhematocrit, and a carefully standardized Coulter F^n for erythrocyte and leukocyte counts. We have stained all blood smears with Wright's stain, counter-stained with buffered Giemsa stain. We have excluded from our series all patients with a mean corpuscular volume (MCV) of 100 cubic microns (cu μ) or more. (Normal Mean $\pm$ 2. Standard deviation = 81.5 to 99.5 cu μ.)

We have arbitrarily set our definition of hypersegmentation at 4 percent or more of neutrophiles with five distinct lobes, connected by filaments, or of any cells with six or more lobes. We have determined the serum folate levels by microbiological assay against cultures of Lactobacillus casei, as described by Herbert.[6] Our normal range is 5 to 21 nanograms (ng) per ml of serum. We have determined serum vitamin B-12 levels by the radio-immunoassay technique of Tibbling,[7] our normal range being 180 to 800 picograms (pg) per ml.

*ADDENDUM: Since submitting this paper, we have changed our folate assay technique to the radio-assay method of Rothenberg et al [Rothenberg SP, DaCosta M, Rosenberg Z: A radio-assay for serum folate—Use of a two-phase sequential incubation, ligandbinding system. N Engl J Med 286:1335-1339, Jun 22, 1972]. In two months with this method, we have encountered ten additional cases of folate deficiency without macrocytosis. Their hemoglobins have ranged from 3.6 to 15.9 gms per 100 ml; their MCV's from 53 to 91 cu μ; their folate levels from 1.4 to 4.3 ng per ml (normal 4.5 to 12.9). All had normal B-12 levels.

TABLE 1.—*Findings in Patients with Hypersegmented Neutrophiles but Without Macrocytosis*

Diagnosis	*Number of Patients*
Positive Cases	45
Folate deficiency alone	29
Folate and iron deficiency	9
Folate and B-12 deficiency	4
Folate, B-12 and iron deficiency	1
B-12 deficiency alone	1
B-12 and iron deficiency	1
Negative Cases	13
Elevated BUN and Creatinine	7
BUN and Creatinine normal	6
Bacterial Inhibitor: No folate assay possible	7
B-12 normal	6
Not tested for B-12	1

Results

Of the 200 patients whose blood smears showed hypersegmented neutrophiles, 65 have subsequently received a reasonably thorough work-up, including tests of folate and B-12 levels and, in many cases, bone marrow examination. On the other hand, in 135 cases, our findings and suggestions were completely ignored. This happened because the patients were receiving cytotoxic drugs capable of producing hypersegmentation (16 cases); because the physician failed to see our note in a bulky clinical record or because the physician felt that the observation of hypersegmented neutrophiles in the absence of macrocytosis must surely be wrong.

Of the 65 patients who had a thorough work-up, seven proved to have a bacterial inhibitor in their serum which interfered with the microbiological assay of folic acid. Of these seven, six had B-12 assays, all of which showed normal levels. Of the remaining 58 patients, 45 proved to have a deficiency of folate, of vitamin B-12 or of both. In 13 patients, no such deficiency could be established. Of the 13, seven had elevated blood urea nitrogren and creatinine levels. Table 1 shows the distribution of findings among the 65 patients who were tested.

Reports of Cases

Case 1. Folate deficiency in acute alcoholic

A 55-year-old chronic alcoholic man was brought to the emergency room by members of the sheriff's department because of impending delirium tremens. On physical examination, the patient was essentially normal except for tremulousness. The spleen and liver were not palpably enlarged.

A blood count done shortly after arrival showed no anemia or macrocytosis. (Hemoglobin [Hgb]: 13.5 grams per 100 ml; MCV: 94 cu μ.) On the smear, however, we found many hypersegmented neutrophiles, and very few platelets. Because of these findings, we encouraged the patient's physician to order tests of serum folate and B-12 levels and a platelet count. The folate level (2.0 ng per ml) and platelet count (19,000 per cu mm) were both low, the B-12 level was normal.

A sternal bone marrow specimen proved to be hypoactive, with early megaloblastic changes in the erythroid cells, and with giant metamyelocytes and banded neutrophiles. Megakaryocytes were sparse, and those found did not appear to be producing platelets. There was distinct vacuolization of the proerythroblasts and myeloblasts. Stainable iron was increased, but we found no ring sideroblasts.

Admitted to hospital, the patient responded to paraldehyde, the hallucinations cleared and tremulousness decreased. Hemoglobin dropped over the next two days, however, as did platelet count, and the stools became guaiac positive. In addition, neutropenia developed. (Leukocytes: 2,000 per cu mm; neutrophiles: 46 percent.) The fibrinogen level was high normal, however, and tests for fibrin monomers and fibrin degradation products gave negative results, thus excluding disseminated intravascular coagulation. After six days of treatment with folic acid, and transfusion of two units of packed red cells, the hemoglobin had risen nearly to normal, the indices remained normal, and the leukocyte and platelet counts had also returned to normal levels. Hypersegmented neutrophiles had disappeared from the blood, and the stools were now guaiac negative. The patient was discharged on the tenth day on folate and multivitamins.

Comment

The demonstration of hypersegmented neutrophiles in a patient without macrocytosis or anemia called our attention to the fact that acute folate deficiency may occur without abnormality in the erythroid series. Such a picture must be common among alcoholics who have not been drinking long enough to develop the macrocytosis of alcoholic liver disease.

Case 2. Folate deficiency in alcoholic

A 58-year-old housewife was admitted to hospital for elective cholecystectomy and rectal polypectomy. For the past five months she had had persistent nausea, had vomited undigested food and had lost 50 pounds of body weight. She complained of inability to eat fatty foods, but stated that she liked and ate leafy vegetables. She admitted being a "binge drinker," however.

A blood count on admission showed normal values (Hgb: 14.2 grams; MCV 95 cu μ; mean corpuscular-hemoglobin concentration [MCHC]: 34.0 percent). There was a shift to the *right* in the neutrophiles, however, and we found appreciable numbers of hypersegmented neutrophiles.

The patient had cholecystectomy and rectal polypectomy without difficulty. On the sixth postoperative day, at a time when the patient was receiving neither vitamin supplement nor antibiotics, the B-12 level was normal (330 ng per ml) and the folate level was much decreased (less than 2 ng per ml). An aspirated bone marrow was normocellular, and showed early megaloblastic changes, most striking in the granulocytes. Marrow iron was normal in amount and distribution. With a diagnosis of inadequate folate intake, presumably a result of her drinking, the patient was discharged on one milligram of folic acid by mouth daily.

Comment

This patient's stores of folate very probably had been impaired by her drinking. The malnutrition associated with the loss of 50 pounds of body weight doubtless had contributed to the deficiency. Finally, the serum folate specimen was obtained after five days in the hospital during which time no solid food and or added vitamins were given. In any case, the finding of hypersegmented neutrophiles signaled an important deficiency.

Case 3. Folate deficiency and uremia

A 60-year-old black man, a retired sign-painter, came to the Medical Clinic because of persistent dizziness and headache. He had been under treatment for about a year for hypertension, receiving reserpine, methyl-dopa, guanethidine sulfate and potassium chloride. Recently, however, his hypertension had become refractory to this treatment. Further, he had developed fatigue on walking one block, and had lost twenty-five pounds of body weight in one year. The patient said that he did not use alcohol.

On examination, blood pressure was 240/120 in both arms. Mucosae were pale. The heart was regular at 85 beats per minute, and was somewhat enlarged on palpation and percussion. The lungs were clear, however, and no dependent edema

was noted. The liver had an overall height on percussion of 11 cm.

A blood count showed a hemoglobin of 6.9 grams; and MCV of 80 cu μ and an MCHC of 32.8 percent. There was modest neutrophilic leukocytosis, with slight left shift. (Leukocytes: 21,200 per cu mm; segmented neutrophiles: 69 percent; banded forms: 8 percent.) On the smear, however, we found a scattering of hypersegmented neutrophiles. Erythrocyte morphology was not particularly abnormal except for a lack of polychromasia. Our note to the patient's record stated that results of blood tests suggested azotemia, with folate deficiency superimposed.

Further laboratory studies showed blood urea nitrogen of 60 mg per 100 ml (normal: 10 to 20): a creatinine of 7.1 mg per 100 ml (normal: 0.7 to 1.4); and a low serum folate (less than 2.0 ng per ml). Normal results were obtained from tests of serum B-12 (800 pg per ml): serum iron and iron binding capacity (62 and 235 mgs per 100 ml; saturation: 26 percent); G-6-PD screen; L-E cell test; direct and indirect antiglobulin test and serum haptoglobin test. On hemoglobin electrophoresis, he proved to have sickle cell trait (Hgb A-S).

An aspirated bone marrow specimen showed normal cellularity with minimal megaloblastic changes, most evident in the granulocytic series. Stainable iron was present in normal amounts, but there were no sideroblasts.

We treated the folate deficiency with orally administered folate, but the azotemia and hypertension proved very resistant to therapy.

Comment

Some degree of hypersegmentation has been reported in many patients with uremic syndrome.[2-5] In this case the malnutrition which had caused a weight loss of 25 pounds doubtless contributed to a real folate deficiency.

Case 4. Iron and folate deficiency

A 21-year-old white school girl was admitted to hospital in acute status asthmaticus, one of many such admissions for this disorder. The patient reported having been given moderate doses of prednisone intermittently for several years, and in recent years had taken antacids because of duodenal ulceration and intermittent bleeding. Her diet was said to be adequate and her menses never excessively heavy. Results of recent stool guaiac tests had been negative. However, she had had persistent microcytic anemia for the past two years.

On this admission, she again showed a low grade microcytic, hypochromic anemia. (Hgb: 11.5 grams; MCV 74 cu μ; MCHC: 31.4 percent.) There was also a modest left shift in the neutrophiles, but there were significant numbers of five- and six-lobed neutrophiles on the smears.

The serum folate level proved to be low (less than 2.0 ng per ml), while the B-12 level was high (over 1,000 pg per ml). Tests of serum iron and total iron-binding capacity (TIBC) established the fact that there was definite iron deficiency. (Serum iron: 20 mg per 100 ml; TIBC: 310 mg per 100 ml; saturation: 6.5 percent.) An aspirated bone marrow showed generalized hyperplasia, with low-grade megaloblastosis, and with complete absence of stainable iron. Our diagnosis was (1) iron deficiency, probably due in part to heavy antacid therapy and (2) folate deficiency, presumably due to malabsorption related to chronic iron deficiency. She was discharged on oral iron and folic acid.

Comment

The apparently very significant folate deficiency was masked in this patient by the microcytosis related to iron deficiency. Such cases are probably by no means rare, as shown by our encountering nine in a period of five months.

Case 5. Folate deficiency in thalassemia minor

A 17-year-old unemployed black man came to the emergency room after being run over by a tractor. Bruises were noted on those parts of his body which the tractor wheel had passed over, and x-ray films of the skull showed a basal fracture. The patient said he did not use alcoholic beverages.

A routine blood count showed a microcytic, normochromic anemia. (Hgb: 11.8 grams per 100 ml; MCV: 67 cu μ; MCHC: 32.2 percent.) On the smears, there were many target and oval red cells, as well as scattered basophilic stippled cells. There also were moderate numbers of hypersegmented neutrophiles. Our note to the patient's record suggested that he be studied for a hemoglobinopathy, as well as for folate and B-12 deficiencies.

Hemoglobin electrophoresis showed type AA, with 3.6 percent Hgb A_2 (normal: 4 percent or less), and Hgb F 1.1 percent (normal: 1.0 percent or less). The serum folate level was definitely

low (2.0 ng per ml), while the B-12 and serum iron levels and iron binding capacity were normal. He refused a bone marrow examination.

Our hematologic diagnosis was (1) thalassemia minor, presumably of beta type and (2) coexistent folate deficiency, presumably due to inadequate dietary intake.

Comment

Just as the microcytosis of iron deficiency may mask any tendency toward macrocytosis, so may megaloblastosis remain hidden behind the microcytosis of thalassemia minor. It was the hypersegmented neutrophiles that led us to suspect folate deficiency.

Case 6. Folate deficiency in early pernicious anemia

A 76-year-old diabetic woman came to the drop-in clinic, complaining of weakness, shortness of breath and swollen ankles, all of one week's duration. She also reported dysuria, and that her urine at times had been bloody. She had been testing her urine for sugar, and what had usually been a 1 plus or 2 plus reaction had recently become 4 plus.

On physical examination, the only abnormal findings were that the liver was palpable 1 centimeter below the costal margin and that there was slight pitting edema of the ankles and feet. Vibratory sense was diminished in both feet, but results of the neurological examination were otherwise normal.

Results of complete blood count were completely normal, but there were significant numbers of hypersegmented neutrophiles on the smears. The fasting blood sugar was 335 mg per 100 ml.

Steps were taken to control the diabetes, and the requested laboratory work was ordered. Surprisingly enough, levels of both serum folate (4 ng per ml) and B-12 (70 pg per ml) were abnormally low. A Schilling test showed a 24-hour excretion of only 1 percent of the orally-administered radioactive vitamin B-12. Results of a second stage Schilling test were normal.

Our diagnosis was early pernicious anemia with some degree of malabsorption of folate, possibly due to the B-12 deficiency.

Comment

Whether the slight decrease in vibratory sensation would have led the clinician to a diagnosis of pernicious anemia is perhaps problematical. The discovery of hypersegmented neutrophiles certainly strengthened any suspicions.

Case 7. Iron and B-12 deficiency

A 75-year-old white man was admitted to hospital because of intermittent right arm weakness and expressive aphasia for the past three weeks. He also reported that there had been bright red blood in his stools for a matter of several months. On physical examination he appeared chronically ill and emaciated. Positive findings were otherwise confined to the neurological examination. There was decreased strength of the right arm, without tremors or fasciculations, and there was hyperreflexia on the right, with a positive Babinski. The rectal examination showed a stool positive for occult blood.

A complete blood count on admission showed a severe microcytic hypochromic anemia. (Hgb: 5.9 grams per 100 ml; MCV; 64 cu μ; MCHC: 27.5 percent.) The leukocyte and differential counts were normal, but again we found scattered hypersegmented neutrophiles. The serum iron studies confirmed the diagnosis of iron deficiency. (Serum iron: 23 mg per 100 ml; TIBC: 290 mg per 100 ml; saturation: 8 percent). The serum B-12, on the other hand, was also definitely low (110 pg per ml), with a normal folate (23.0 ng per ml). A bone marrow examination showed definite megaloblastosis, and a complete lack of stainable iron. The Schilling test showed no excretion of radioactive B-12 in 24 hours.

A barium enema examination showed a carcinoma of the colon at the hepatic flexure, while a brain scan showed an area of decreased perfusion in the left hemisphere, interpreted as indicating obstruction of the left middle cerebral artery.

The patient had hemicolectomy with transverse colostomy. No metastases were found on operation, and the post-operative recovery was satisfactory. We treated the blood picture with intramuscularly administered B-12 and oral iron, and the patient responded well. Results of a subsequent second stage Schilling test were normal at 15 percent excretion.

Comment

The severe iron deficiency in this old man, due to carcinoma, thoroughly masked the fact that he also had pernicious anemia. If the hypersegmented neutrophiles had not been found, the vitamin B-12 deficiency would probably have gone unrecognized for some time.

Case 8. Deficiency of iron, folate and B-12

This 52-year-old white woman was brought to the emergency room by her husband who had found her lying in a pool of blood on the kitchen floor. She had an eight-year history of a seizure disorder, for which she was receiving primidone. She and her husband both stoutly denied alcoholic intake. She complained of chronic diarrhea, worsened by eating green vegetables. She had lost weight from 115 to 93 pounds in the past two years.

On physical examination, laceration of the scalp was noted, but there was no evidence of fracture. Neurological examination showed hypertonic deep tendon reflexes in all extremities, and positive Babinski's bilaterally. Vibratory sense was lacking in both legs to the knees, and was sub-standard at the hips.

An initial blood count showed a normocytic, normochromic anemia. (Hgb: 7.3 grams per 100 ml; MCV: 84 cu μ; MCHC: 32.2 percent.) There was a shift to the right in the neutrophiles (banded cells: 0 percent), and many large, hypersegmented cells were found on the smears. We therefore determined the folate (2.0 ng per ml) and B-12 (80 pg per ml) levels, both proving abnormally low. Her serum iron and saturation were likewise low. (Serum iron: 23 mg per 100 ml; TIBC: 405 mg per 100 ml; saturation: 5.5 percent.) A bone marrow specimen obtained by sternal puncture, was frankly megaloblastic, and contained no stainable iron.

Our diagnosis, then, was a triple deficiency of folate, vitamin B-12 and iron, presumably due to some as yet undiagnosed malabsorption syndrome. A Schilling test showed 4.6 percent excretion of orally administered radioactive B-12 in 24 hours (normal: 7 percent or more). The patient, however, refused to undergo the second stage Schilling test, or any further testing of the gastro-intestinal tract, but insisted upon returning to the care of her family physician. The latter, on our advice, agreed to see that she received regular injections of vitamin B-12, folate and iron.

Comment

In this unusual case, it was the finding of hypersegmented neutrophiles which led directly to the further work-up, and to the discovery of the triple deficiency. The extent to which primidone might be contributing to the diarrhea, the neurologic disorder or even the megaloblastosis has not been determined.

Discussion

We undertook this study anticipating that we would discover an occasional case of folate deficiency, largely among alcoholics. We were not particularly surprised at the failure of many of our colleagues to follow our suggestions regarding further laboratory investigation. The fact of folate or B-12 deficiency without macrocytic anemia has indeed received very little attention.

We were surprised to find, among the 58 patients who were adequately studied, and who did not have a bacterial inhibitor which interfered with the folate assay, that 43 had a definite folate deficiency. Even more surprising were the seven who proved to have a low vitamin B-12 level. This experience indicates to us that the additional effort required to look carefully for hypersegmentation is thoroughly justified in the additional help the laboratory can give the clinician.

We were particularly interested in the 13 patients in whose blood we found hypersegmentation, but whose serum folate and B-12 levels proved normal. Some may have had blood specimens for folate determination drawn sufficiently long after the start of a nutritious hospital diet that a formerly low folate level had come into the normal range. Seven of the thirteen, however, proved to be uremic to at least some extent, suggesting that uremia must be included in the differential diagnosis when hypersegmentation is encountered in the absence of macrocytosis.

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Adenocarcinoma of the Colon and Rectum

ALLAN J. WAGMAN, MD, *and* WILLIAM H. KERN, MD, *Los Angeles*

The site and the sex incidence of 555 carcinomas of the colon surgically resected at The Hospital of the Good Samaritan in Los Angeles were reviewed. Most of the carcinomas of the right and transverse colon were in female patients, and slightly more than half of the cancers of the left and rectosigmoid were in male patients. The largest tumors were found in the right and transverse colon. The incidence of carcinomas in the proximal colonic segments, especially the cecum, appears to be greater in patients of middle or upper socioeconomic groups, a phenomenon possibly related to diet.

According to the American Cancer Society there will be about 99,000 new cases of cancer of the colon in 1974, a number greater than the estimates for either breast or lung cancer.[1] Furthermore, 48,000 patients are expected to die of cancer of the colon and rectum, a figure exceeded only by estimated deaths due to lung cancer.

The location of the tumors within the colon influences the survival rate[2] and also may be related to the socioeconomic status of the patient or other environmental factors.[3,4] Most of the reported cases of colorectal cancers are in patients of a kind generally treated in county hospitals. To cast further light on this factor we undertook a study to evaluate incidence data in a large private hospital and to compare these findings with those observed at other centers.

From the Department of Pathology, The Hospital of the Good Samaritan, Los Angeles.

Submitted March 27, 1974.

Reprint requests to: W. H. Kern, MD, Department of Pathology, The Hospital of the Good Samaritan Medical Center, 1212 Shatto Street, Los Angeles, CA 90017.

Materials and Methods

The pathologists' reports on surgical specimens in all cases of adenocarcinoma of the large bowel in which resection was done at The Hospital of the Good Samaritan, a 400-bed private hospital in downtown Los Angeles, were examined specifically for the location and size of the tumor, the presence of polyps, and the sex of the patient. From January 1, 1964, to December 31, 1973, colectomy was done in 588 cases. The information in 33 of the reports was incomplete. We evaluated the remaining 555 cases.

Results

Distribution of the 555 adenocarcinomas is shown in Figure 1. About 57 percent of the cases were located in the rectosigmoid colon and 17 percent in the cecum. Table 1 shows a striking difference in the distribution of cancers in male and female patients. Of the 257 male patients, 167 (65 percent) had tumors located in the

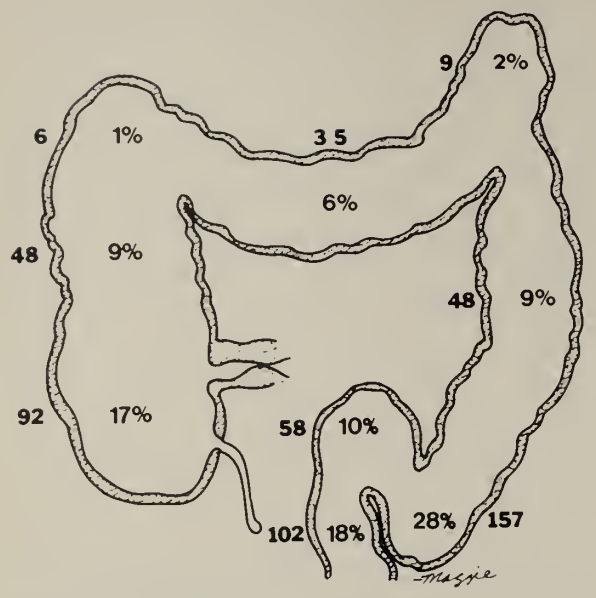

Figure 1.—Distribution of 555 adenocarcinomas of the colon.

sigmoid colon or rectum, whereas only 150 (50 percent) of the 298 female patients were found to have tumors in this region. On the other hand, over two-thirds of the 92 cancers of the cecum, and all but nine of the 50 carcinomas of the transverse colon occurred in females.

As shown in Table 2, the resected carcinomas varied considerably in size, measuring from 1.5 to 15 centimeters in greatest diameter; generally, the larger tumors were located in the right colon and the smaller tumors in the left colon. There was no significant difference in size between tumors of the descending colon and of the rectosigmoid.

In 52 (9 percent) of the cases studied, the cancer was polypoid or arose in a villous adenoma or adenomatous polyp. In addition, one or more benign polyps were found incidentally in 83 (15 percent) of the 555 colons that were removed. There were multiple primary carcinomas in five cases.

Discussion

Table 3, a comparison of our results and those of seven other institutions, shows that an above average proportion of carcinomas seen at The Hospital of the Good Samaritan were located in the cecum, and a below average proportion in the rectum. This distribution of colorectal tumors is very similar to that reported from the Mayo Clinic, but different from that seen in the large public hospitals. This may be related to the fact that patients admitted to the Mayo Clinic and The Hospital of the Good Samaritan generally belong to the higher socioeconomic groups. It has been demonstrated in New York City that upper socioeconomic groups have a higher death rate from colon cancer.[3] Furthermore, with the exception of Japan, the incidence of colon and rectal cancer is greater in the industrialized countries of the world, where the higher socioeconomic groups reside.[5] In the countries with a relatively high risk of colorectal cancer, the diet has a low bulk content because the unabsorbable fibrous material is frequently refined or boiled out of the food. Low stool bulk results in a prolonged transit time through the bowel.[5]

While little difference in the distribution of cancer in males and females was found by Lanier et al[6] at the Mayo Clinic, other investigators have reported findings similar to ours. MacLeod et al[7] reported a significantly greater rate of cancer in female patients in the right and middle colon and

TABLE 1.—*Distribution of Cases by Sex*

Sex	*Cecum*	*Right*	*Transverse with Flexures*	*Left*	*Sigmoid*	*Rectosigmoid*	*Rectum*	*Total*
Male	30	27	9	24	81	34	52	257
Female	62	21	41	24	76	24	50	298
Totals	92	48	50	48	157	58	102	555

TABLE 2—*Distribution by Size of the Macroscopic Cancers*

	(Largest Cross-Section Diameter Measured in Centimeters)						
Size	*Cecum*	*Right*	*Transverse with Flexures*	*Left*	*Sigmoid*	*Rectosigmoid*	*Rectum*
Largest	13.0	13.0	15.0	10.0	10.0	9.0	8.0
Smallest	2.0	2.8	2.5	1.5	1.5	1.5	1.5
Average	6.2	5.6	5.5	4.5	4.5	4.2	4.7

TABLE 3—*Comparison of Results*

Hospital	Location in Colon in Percentage*						Percentage with Benign Polyps
	Cecum	Right	Transverse with Flexures	Left	Sigmoid	Rectum	
Massachusetts[10] 1962	10(179)	6(117)	10(194)	5(94)	27(511)	41(771)	..
Charity[11] 1966	10(147)	5(75)	12(184)	4(70)	23(365)	46(707)	11.6
University of Virginia[12] 1968	11(53)	6(27)	12(58)	5(25)	23(111)	43(208)	..
Cornell[13] 1969	8(131)	5(77)	11(198)	4(65)	19(315)	53(868)	9.5
Middlesex[8] 1971	8(53)	3(21)	10(67)	5(33)	22(141)	52(341)	24.5
Saskatchewan[9] 1972	9(97)	8(92)	11(119)	6(61)	22(247)	44(487)	15.0
Mayo Clinic[6] 1972	16(70)	9(37)	12(53)	4(19)	25(107)	34(150)	25.0
Good Samaritan† 1974	17(92)	9(48)	9(50)	9(48)	28(157)	28(160)	15.0
Totals	10 (822)	6 (494)	11 (923)	5 (415)	23.5 (1954)	44.5 (3692)	

*Number of cases in parentheses. †Wagman, Kern.

a slight predominance of cancer in the rectum in males. In a study from Middlesex Hospital in London there was a predominance of both cecal and transverse lesions in women and a slight predominance of rectal lesions in men.[8] On the other hand, Weir[9] reported no ascending colon cancer sex difference in his Saskatchewan group, but he did find the incidence of cancer of the transverse colon twice as high in women as in men.

There is general agreement that tumors located in proximal portions of the colon are larger than those located in the rectosigmoid.[8] The reason for this may be the late onset of symptoms, which may be attributable to three factors: First, the fecal material is still liquid in the right colon; second, the bowel has a relatively large circumference in this area and, third, the bleeding from a cancer may not be readily discovered. We could find no evidence to suggest that there might be intrinsic differences in growth rates of carcinomas associated with location in the colon.

The presence of adenomatous polyps in 15 percent of the resected colons in our study corresponds roughly with data reported in other series (Table 3). Like other investigators, we found carcinomas which had developed in pre-existing villous adenomas, as well as in adenomatous polyps.

Burkitt[5] suggested that cancer may be the result of prolonged stool contact on the bowel mucosa. This theory might explain the differences between the various socioeconomic groups, whose members do consume varying proportions of bulk in their diet. However, it is doubtful that diet alone could explain the sex variations reported.

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Parkinson's Disease and Levodopa

A Five-Year Follow-up and Review

CHARLES H. MARKHAM, MD, LEO J. TRECIOKAS, MD, *and* SHIRLEY G. DIAMOND, BA
Los Angeles

NOT ONLY HAS LEVODOPA shown itself to be the best therapeutic tool we have in Parkinson's disease, it has also led to a much better understanding of the disease and of basal ganglia function.

Clinical-Pathological Findings

The clinical state we call Parkinson's disease is usually one of the easiest neurological diagnoses we make. The mean age of onset of Parkinson's disease (paralysis agitans, defined below) in the present series is 54.2 (n = 82, range 32 to 76), and this is very similar to that noted in other series.[1] Men are affected twice as often as women. The disease, at least when treated by older methods, progressed to death in 9.4 years (range 1 to 33).[1] There are at least two of three major symptoms:

1. Tremor, beating at 3 to 6 per second, often first attracts attention but usually is the least disabling. It occurs in a limb, or less commonly in the trunk or face when that part of the body is at rest. It tends to be damped by a movement or change of posture.

2. Rigidity is an increased resistance of the flexor and extensor muscles to either active or passive movement. The patient may say his arm, for example, feels stiff or heavy or awkward and it has a dull ache. The physician can detect an increased muscular resistance as he manipulates the relaxed extremity.

3. Akinesia consists of a lack of movement and also a hesitancy or interruption in the performance of certain movements (see Markham, 1973[2]). Akinesia may cause inexpressiveness of the face or a loss of minor limb and trunk movements. The person moves awkwardly and a movement may be interrupted in midcourse. Akinesia usually becomes the most disabling symptom.

There are also other symptoms, some of which may stem from those already listed—low amplitude or hesitancy of voice, seborrhea, drooling of saliva, flexed posture, and small handwriting. While not strictly a part of the parkinsonian state, two other symptoms that are occasionally seen are depression and slowly progressive organic dementia. More will be said about these later.

These symptoms may be due to the disease James Parkinson first described in 1817,[3] and which we now call paralysis agitans, or Parkinson's disease, or primary parkinsonism. This is the most commonly occurring type today. Its cause is unknown. Or these symptoms, plus certain others such as dystonic distortions of posture and oculogyric crises, may be secondary to encephalitis. This post-encephalitic or secondary parkinsonism followed the influenza pandemics after World War I. It is rare today but may still occur after certain virus infections. Secondary parkinsonism may also be due to carbon monoxide intoxication;[4,5] manganese poisoning;[6,7] several small strokes or vascular lesions (this is sometimes called arteriosclerotic parkinsonism); or small lesions of the basal ganglia such as a tuberculoma of the substantia nigra.[8] Parkinsonian

From the Department of Neurology, University of California, Los Angeles, School of Medicine.
Reprint requests to: C. H. Markham, MD, Department of Neurology, University of California, Los Angeles, Center for the Health Sciences, Los Angeles, CA 90024.

symptoms may be a part of a more widespread disease such as progressive supranuclear palsy[9,10] or striatonigral degeneration.[11-13] Some of these have other symptoms, or manner of progression, but some, such as striatonigral degeneration, may be quite indistinguishable from paralysis agitans.

One or more of the main symptoms of Parkinson's disease, or something closely resembling them, may appear in certain other neurological diseases. Rigidity and akinesia may occur in Jakob-Creutzfeld disease, the rigid form of Huntington's chorea, and in Wilson's hepatolenticular degeneration. The postural and intention tremor of familial (or essential) tremor may be confused with that of Parkinson's disease. Some of the treatment failures of levodopa or other remedies are due to failure to correctly diagnose Parkinson's disease.

The neuropathological abnormalities in parkinsonism, as identified with classical staining techniques, center on the substantia nigra. In paralysis agitans the large pigmented nigral neurons are reduced and some of the cells remaining have intraneuronal inclusions (Lewy bodies).[14] In addition to the nigral lesions, neuronal and glial abnormalities are very common in the globus pallidus, cortex and somewhat less common in the cerebral and cerebellar cortex and elsewhere throughout the central nervous system.[15] These widespread changes may be essentially those of senility[16] but their frequency and the frequency of their clinical manifestations (for example, organic dementia) suggest they may have a more central role in Parkinson's disease.[17]

The pathological changes in postencephalitic Parkinson's disease consist of more severe loss of pigmented neurons in the substantia nigra, Alzheimer's neurofibrillary tangles in many of the remainder. There may also be changes in the globus pallidus to such an extent that at least one present-day investigator felt this was the main lesion.[5] See Forno and Alvord[17] for a careful recent review.

Some Anatomy and Histochemistry

Certain regions of the central nervous system have particular relevance to Parkinson's disease. The substantia nigra has large neurons which contain enough melanin to give the nigra a blackish-gray appearance in the freshly cut brain. Extraordinary work over the last 15 years has shown that these melanin-containing cells contain dopamine,[18,19] and that dopamine is transported via unmyelinated axons of minute diameter (0.1 to 0.2 microns)[20] to synaptic terminals in the putamen and caudate nuclei (together termed the striatum).[18,19] (There is another non-dopaminergic nigrostriatal pathway which is not considered in this article.) Dopamine is also formed in the terminals themselves. Dopamine is decidedly reduced in the substantia nigra in Parkinson's disease.[21] Extrapolating from work in rats where normal dopamine in the striatum is still present after degeneration of 25 percent of dopaminergic fibers, it probably takes moderate loss of nigral cells in man to produce clinical signs.[22]

The striatum was not considered significant in the pathophysiology of Parkinson's disease until about 15 years ago. This was because no lesions could be seen and because the nigrostriatal path was too fine to be seen by ordinary light microscopy. However, the connection was established when dopamine was shown to have much the highest concentration in the nervous system in the striatum,[23,24] and striatal dopamine was decidedly reduced in Parkinson's disease.[25] (See Chart 1.) Further, L-dopa decarboxylase, the dopamine synthesizing enzyme, and homovanillic acid, the main dopamine metabolite, are diminished in the striatum in Parkinson's disease.[26]

In broad brush strokes, the main steps in dopamine neurotransmission are as follows. (See Carlsson, 1971[27] for a further review.) Dopamine is decarboxylated from levodopa within the nigrostriatal neuron and is held in storage vesicles in the synaptic terminal. Free dopamine within the nigrostriatal neuron is apparently degradated by the mitochondrial enzyme monoamine oxidase (MAO). The nigrostriatal neuron, in response to stimulation, releases dopamine into the presynaptic cleft. Multiple branching of the dopaminergic axons suggests one nigral cell acts on many striatal neurons, probably the middle-sized spiny neurons (see below). Several lines of evidence suggest dopamine acts on the receptor sites in these cells in such a way that the firing of the cells is inhibited. After presumably causing a brief hyperpolarization of the receptor cell, the dopamine is released from the receptor site to be either taken up into the presynaptic terminal for re-use or inactivated (O-methylated) by catecholamine methyl transferase (COMT). In sum, stimulation of the nigral cells, probably in the nigra itself, inhibits many of one class of striatal cells.

The striatum contains other neurotransmitters

which are either altered in Parkinson's disease or in the treatment thereof: acetylcholine (Ach), gamma amino butyric acid (GABA) and serotonin. Ach concentration in the striatum is significant,[28,29] as is the activity of acetylcholinesterase and choline acetylase, its inactivating and activating enzymes respectively.[30] Striatal Ach is localized in nerve endings, or at least in the subcellular fraction on ultracentrifugation which contains synaptic vesicles.[31] It now appears the cells of origin of these Ach-containing synaptic terminals are one of the caudate interneurons, for damaging the areas which project to the striatum, the thalamus, cerebral cortex and ventral midbrain tegmentum,

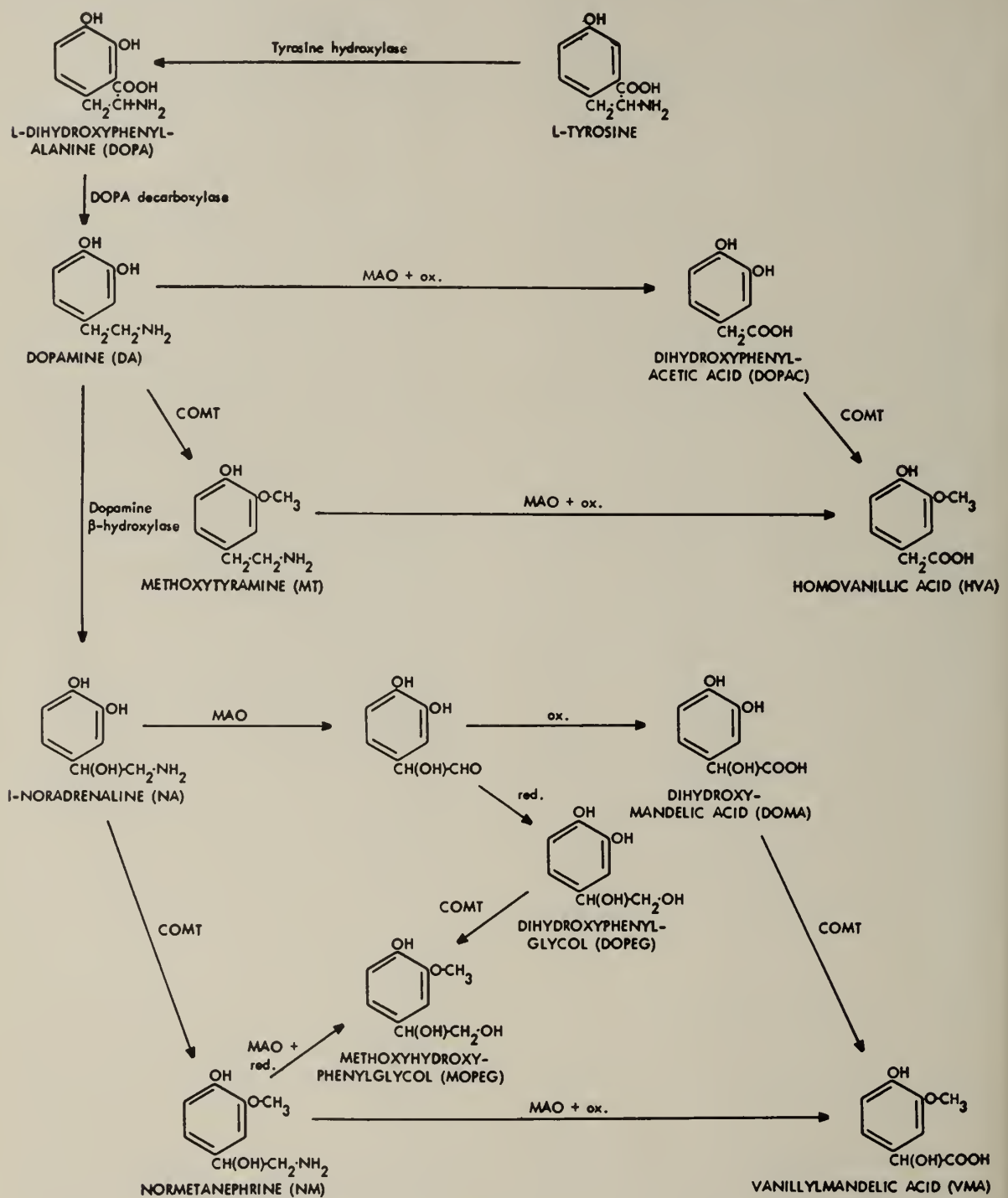

Chart 1.—The main biochemical pathways of levodopa.[27] Reproduced with permission of F. A. Davis Co.

do not alter the striatal choline acetylase and cholinesterase.[32] Further, choline acetylase activity is reduced about 50 percent in Huntington's chorea, a disease with major loss of striatal neurons.[33] While Ach, or its forming or inactivating enzyme, has not conclusively been shown to be abnormal in Parkinson's disease, it is clear that anticholinergic drugs benefit parkinsonian symptoms. If this effect is due to action in the striatum and not elsewhere in the nervous system, it suggests that decreased striatal dopamine in this disease may allow a class of striatal Ach interneurons to be relatively overactive; and anticholinergic agents partially correct this imbalance.

GABA and its forming enzyme, glutamic acid decarboxylase (GAD), are also important in striatal function. In untreated Parkinson's disease, GAD activity is reduced in the striatum to less than 50 percent of the control mean,[34,35] while in Parkinson's disease chemically treated with levodopa, it is normal. In Huntington's chorea, a disease with massive degeneration of striatal neurons, GABA is low in the striatum, in the globus pallidus and in the substantia nigra,[36] and GAD activity is 80 to 90 percent reduced in the first two sites (that in the nigra was not measured).[33] This, coupled with recent anatomical findings in the striatum (see below) suggests that GABA may be formed and released in another class of interneurons in the striatum, and that parkinsonian nigral-striatal dopamine deficiency may lead to the lowered GAD activity. GABA appears to be an inhibitory neurotransmitter in the central nervous system.[37,38]

Serotonin is still another neurohumor (neurotransmitter?) in the striatum which is mildly decreased in Parkinson's disease.[39] Serotonin is concentrated in nerve cell terminals and is converted there from its precursor by 5-hydroxytryptophane decarboxylase, which is apparently the same enzyme as dopa decarboxylase. The cell bodies of the serotonin neurons lie in the midbrain and pontine raphé nuclei not far from the dopaminergic neurons in the midbrain.[18] It is not known why serotonin is decreased in the striatum in Parkinson's disease, but it may be from death of some of these cells which have many features in common with dopaminergic ones. Administration of 5-hydroxytryptophan, the precursor of serotonin, which unlike serotonin crosses the blood brain barrier, either does nothing for human parkinsonian symptoms[40] or makes them somewhat worse.[41]

It is now possible to look a little closer at the cellular makeup of the striatum, keeping in mind that in most cases of Parkinson's disease death occurs to the dopaminergic cells in the substantia nigra but that many symptoms are attributable to failure of dopamine to be delivered to specific sites in the striatum. The striatum has several morphological cell types, described in Kemp and Powell's series of articles.[42-46] The medium spiny, short-axon cell has many, many spines on its branched dendrites. The dendritic spines constitute the most frequent type of post-synaptic contact, but there are also synapses on the proximal dendrites (bare of spines), on the cell body and on the initial segment of the axon. The axons are very short, and have many branches which do not extend beyond the arborization of the dendritic tree. These cells are interneurons. About 96 percent of the striatal cells are medium spiny cells. There are also 1 to 2 percent of other short-axoned cells.[42]

The medium size long-axon cell and the giant cell both have long axons which extend outside the caudate and putamen. Some of the axons of these cells have collaterals. These cells are the only efferent cells of the striatum and constitute about 2 percent of the striatal cells. These studies do not reveal how the many medium spiny cells presumably converge on the striatal efferent cells. The axons from the striatum project to the globus pallidus (which in turn projects to the nigra, to other midbrain sites and to the thalamus) and to the substantia nigra[47] (see Figure 1). The striatonigral neurons send collaterals into the globus pallidus, cause inhibition of both nigral and pallidal cells, and are apparently GABAnergic.[48-50]

Electron microscopic study of degenerating presynaptic terminals showed that after lesions of the cortex or the thalamus or a combination of the two, or of the midbrain, there were degenerating endings mostly on dendritic spines and only a few on main stem dendrites and cell bodies.[44] A Golgi study preceded by lesions of the thalamus, cortex or both showed the cortex and the thalamus had afferents to the striatum which terminated on the same medium sized spiny cells.[45]

The above studies did not reveal 0.1 to 0.2 micron unmyelinated axons, coming from the midbrain (that is, the presumably dopaminergic path) on their synaptic terminations. However, Hattori et al,[20] by using electron microscopy combined with autoradiography, were able to show dopaminergic terminals ending on dendritic spines (and thus, probably, these were medium sized spiny cells).

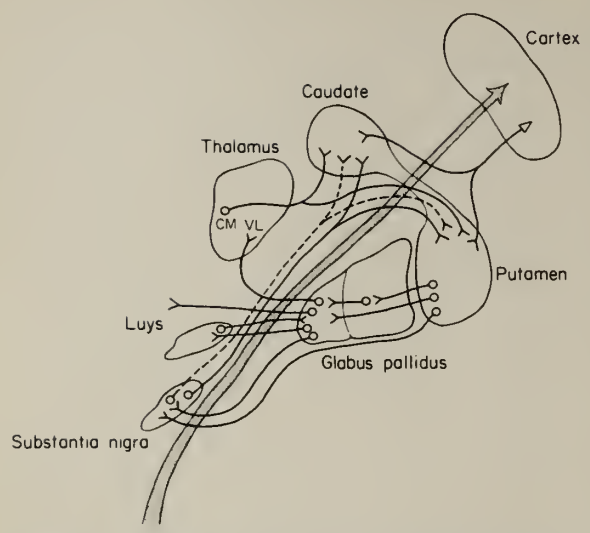

Figure 1.—Diagram of the basal ganglia and some of the pathways referred to in the text. The broad pathway descending from the cortex represents the internal capsule. The nigrostriatal path is shown by a solid line and terminates in both the caudate nucleus and the putamen. The caudate projects to the globus pallidus and substantia nigra but only those from the other part of the striatum, the putamen, are shown.

At the risk of oversimplification, one might conclude:

1. There are at least four inputs to the striatum (from the cortex, the thalamus, and two from the substantia nigra), with neurotransmitter known only for the nigral dopaminergic path.

2. From the neurochemical standpoint, some striatal interneurons may produce and release GABA as a neurotransmitter while other interneurons release Ach.

3. From the morphological standpoint, the medium sized spiny neurons are interneurons and constitute about 96 percent of the striatal cells. It is not known how these cells interact or in turn act on the long-axonal striatal efferent cells.

4. The major sources of afferents to the striatum—the cortex and thalamus—terminate largely on dendrites of the medium spiny cells, often on the same cells. The dopaminergic cells in the nigra send axons to the striatum which branch repeatedly before terminating on cells with dendritic spines. These cells might or might not be the same ones as those receiving thalamic or cortical terminations.

Response to Injury of the Substantia Nigra

When a lesion is made in the substantia nigra in an experimental animal, some cells die, others have their axons going to the striatum and elsewhere severed, and striatal dopamine content decreases according to the size of the nigral lesion. Then several things of interest happen:

1. Vigorous sprouting of the remaining, or possibly damaged dopaminergic cells takes place in the region of the injury, and nearby areas receive many terminals filled with dopamine. Many aberrant sites such as capillaries, scar tissue (and possibly neurons which did not have dopaminergic terminals?) receive such terminations.[51]

2. With loss of some striatal endings following death of their distant cell bodies in the nigra, some post-synaptic terminals become vacated; and neighboring intact nigrostriatal presynaptic endings may sprout and cover them. While sprouting in this particular circumstance has not been demonstrated, it seems possible in view of the very vigorous sprouting found within central catecholamine-containing neurons.[52] Further, dependent on the pattern of loss of presynaptic terminations, there might be post-synaptic sites with either too few or too many new sproutings. Therapeutically elevating the brain content of dopamine by giving large amounts of levodopa could either do little good, or help certain symptoms, or produce signs of local overdosage (choreoathetosis, see below).

3. It has now been clearly shown that two fiber systems converge on certain neurons in the rat septum. When nonadrenergic ones from the hippocampus are eliminated by cutting the ipsilateral fimbria, many synapses on dendritic spines undergo orthograde degeneration. After one month almost all dendritic spines appear to be re-innervated.[53,54] The source of re-innervation appears to be the medial forebrain bundle, which contains a number of ascending catecholaminergic fibers, some of which go to the septum. Paralleling the histological changes above, there are increases in septal norepinephrine and histofluorescence of the norepinephrine type.[52]

If similar aberrant re-innervation took place in Parkinson's disease, we might expect to find striatal (or midbrain?) terminals, formerly dopaminergic, now re-innervated by Ach or serotoninergic[55] endings.

Some of the variations in clinical symptoms or in therapeutic response to different drugs may be due to such variations in regrowth (see below).

4. Some of the sprouting terminals may make the "wrong" neurotransmitter—for example, norepinephrine.[51] Further, serotoninergic terminals, regenerating or not, appear to be able to convert dopa to dopamine.

5. When there is partial degeneration of dopaminergic nigrostriatal pathways in the rat, there is hyperactivity of the remaining dopaminergic neurons.[22] This compensating mechanism may also be a factor in human parkinsonism.

Clinical Efficacy of Levodopa

The many complications and subtleties in the use of levodopa in Parkinson's disease implied in the previous sections of this paper were not evident when dopa was first tried[56-58] or in the early well studied series.[59-64] What became clear after a year or so of treatment was that more than half the patients with disease of all degrees of severity were decidedly improved, some to the point of being symptom free. Most of the remainder benefited to some degree, and side effects such as nausea and vomiting, choreoathetosis (a new etiologic factor for this movement disorder), postural hypotension, and organic confusion were often troublesome but never lethal. Now after five years we are in a position to give a more long-range view.

Our own series has consisted of a nucleus of 100 patients first started on levodopa in 1968 and early 1969, and thus followed for at least five years. We have added to this another fifty or so patients who participated in special studies or who presented special problems, plus about another fifty who were seen in consultation or for a few visits with problems relatively simple to manage.

Our initial group had about the same vital statistics as patients in most other series. Of 93 patients (seven dropped out in the first year), 65 were men and 28 were women (this 2:1 ratio is usually observed); 81 had paralysis agitans (Parkinson's disease of unknown cause) and 11 had postencephalitic parkinsonism; one had atypical parkinsonism secondary to an en plaque meningioma. The duration of disease at entry into the study for the paralysis agitans patients was 9.8 years (range 2 to 31), while for the postencephalitic group it was 17.2 years (range 5 to 30). The age at onset was 54.3 years (range 27 to 76) for the paralysis agitans group and 31.6 years (range 16 to 54) for the postencephalitic group. The degree of the parkinsonism ranged from mild to severe (see below). Twenty-four had organic mental confusion before the start of the study; 71 were depressed. The patients making up this group differed from random patients with Parkinson's disease in two respects: They were motivated to try a new drug, and they showed more persistence in continuing the use of levodopa through sometimes trying side effects.

The severity of the disease and its effect on the person's life were measured in two ways:

1. Eleven signs and symptoms (rigidity and speech disability, for example) and nine activities (dressing, handwriting and the like) were given values weighted as to how much a given symptom interfered with daily living, and this figure then was multiplied by a number representing the severity of that symptom. These were summed and compared with the same evaluation before treatment began. (See Treciokas et al[63] for more details).

2. Parkinson's disease was given a I to V rating (I, mild unilateral symptoms; V, complete invalidism[1]). Both systems were judged by what the examining physician could see or test, except for a few items (for example, use of toilet, turning in bed).

The above examinations, plus partial general physical examinations, blood pressure supine and erect, and other examinations[63] were done at one to three month intervals. Other antiparkinsonian measures were initially continued but since then we have attempted to withdraw or change these in most patients (see below).

Our practice, then as now, was to start with 500 mg of levodopa per day, and then increase this amount every fourth or fifth day until a daily dose of 3.0 grams was reached. A more gradual increase was then carried out to a maximum of 8.0 grams daily or until significant side effects occurred. Later we gave several patients as much as 10.0 grams daily. The daily dose was divided into four to six allotments.

As is now well known, the beneficial effects usually start appearing after a few weeks and then show continuing improvement for as long as a year. Usually the good effects reach a maximum at about six months. A few patients lose some of their initial improvement and then level off at a lower level of improvement. By one year, the mean disability scores had fallen considerably (see Chart 2), and the stage of disease had changed from a mean of 3.1 to 1.75 (Chart 3). Relative to the initial state, the group as a whole showed about a 50 percent improvement. Chart 4 shows a parallel between the two measures of disability. The 50 percent improvement for the whole group encompassed 10 percent of patients who were

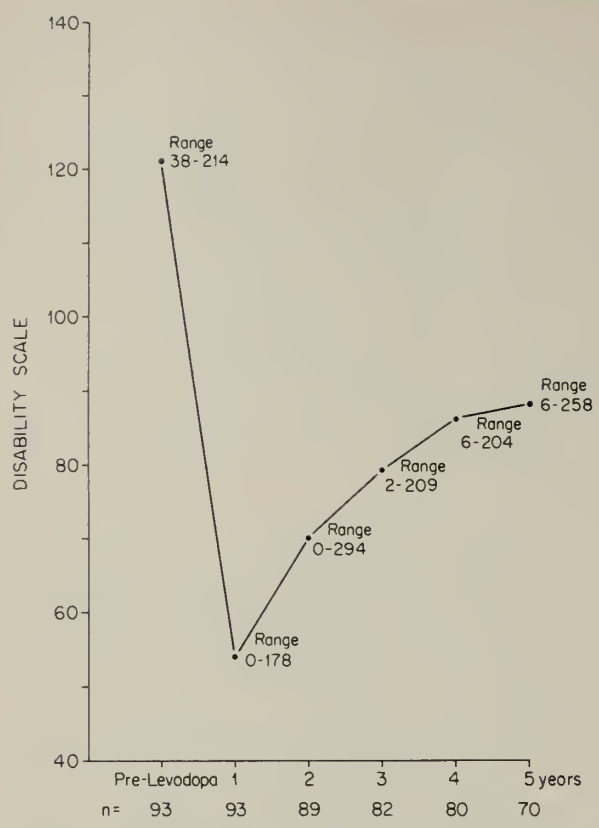

Chart 2.—Mean disability scores. Scale consist of 11 signs and symptoms and 9 activities, each weighted 1 to 10 according to degree of interference in daily ilfe, and multiplied by degree of severity (absent=0, mild or moderate=1, marked or severe=2). Maximum score possible is 440.

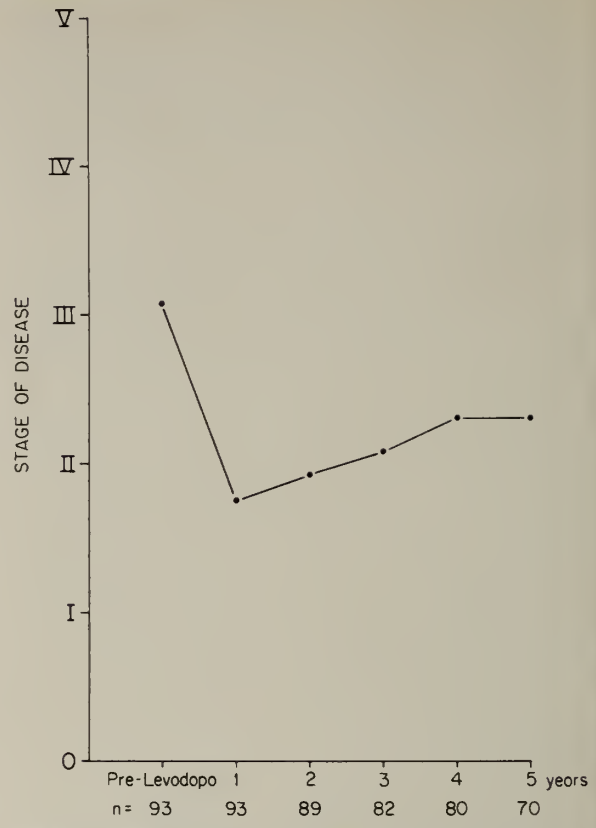

Chart 3.—Mean stage of disease. Hoehn and Yahr's[1] classification system in which I=unilateral involvement only, II=bilateral involvement, III=impaired postural and righting reflexes, IV=marked disability, V=confined to bed or wheelchair.

symptom-free as long as they took their medication, and about 10 percent who were worse or had minimal improvement. Five years of follow-up has been completed for 70 patients. Let us consider what has happened over that five-year period. We are still following 73, but three have not yet reached a full five years of therapy. Of the remaining, 11 have died (see below); three are in nursing homes because of severe dementia and are not receiving levodopa; and two are completely bedridden because of a broken hip and a stroke, and cannot be evaluated for parkinsonism. Four patients have been lost to follow-up because they have moved away.

As Charts 2, 3 and 4 show, both measures of the stage of disease show an increasing amount of disability in the second, third and fourth years from the levels reached in the dramatic improvement of the first year. There is a suggestion of levelling off at 25 percent improvement over their initial condition by the fifth year. When we look at individual cases at the fifth year, six patients (9 percent) are nearly symptom-free (disability scores under 20). All of these patients are in Stage I. Others (six patients, 9 percent) are worse than they were at the beginning of the five-year levodopa trial. In spite of the generally increasing disability over the last four years, it should be noted that most of the patients have fewer parkinsonian symptoms and are more able than they were before the study began.

The individual signs and symptoms of Parkinson's disease were qualitatively much the same as before and at one and five years of levodopa therapy. Thus if the patient had tremor, mask-like face and small handwriting before therapy, the same symptoms, usually improved, were present at five years. If one symptom was going to cause major trouble at five years, it was not responding well to levodopa therapy at one year. A patient who had persistent tremor at one year continued to have tremor at five years. A patient

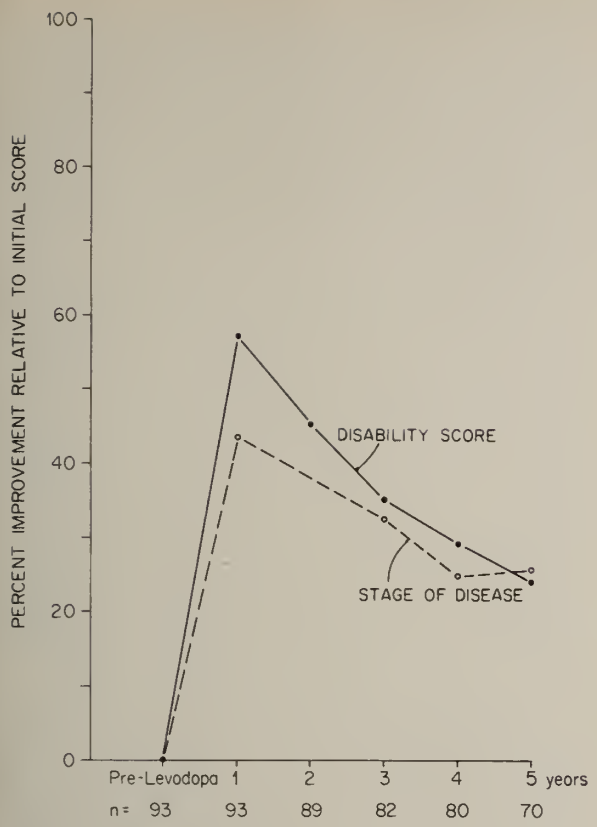

Chart 4.—Mean improvement in stage of disease and disability scores. The graph of the Stage of Disease shows the group mean at each year, expressed as percent improvement compared with the pre-levodopa group mean. The graph of the Disability Score is derived by taking each patient's score, converting it to percent improvement compared to his own pre-levodopa score, and the mean for the group taken for each year.

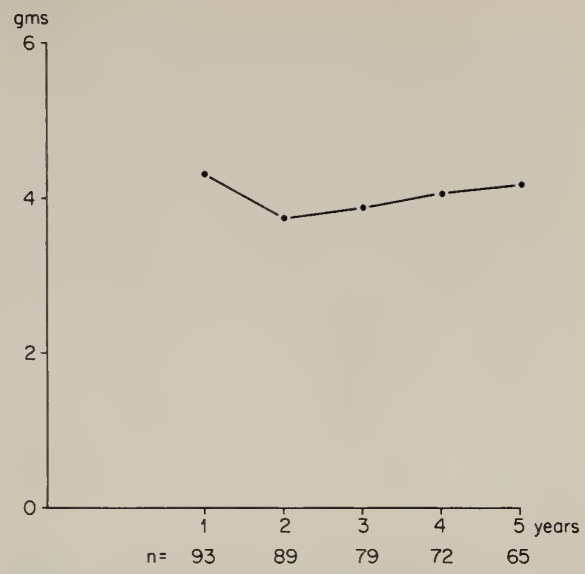

Chart 5.—Mean dose of levodopa. Number of patients shown in years 3, 4, and 5 do not include those taking dopa decarboxylase inhibitors in combination with low levodopa dosages: one patient in year 3, eight in year 4, five in year 5.

who had a good response at one year except for sudden unexpected falls, was still having the falls at five years. Similarly, if a symptom such as akinesia was well controlled at one year it was likely to be well controlled at five years.

The loss of improvement seen at five years relative to one year is due to several things. In some instances it is a clear progression of parkinsonian symptoms—more resting tremor, worsening of voice in a characteristic parkinsonian way, an increase in rigidity. In other instances such as walking a little more slowly, or more trouble climbing stairs, it is hard to know if it is due to parkinsonism or the effects of five years' aging on other parts of the neuromuscular system. In still other instances, increasing disability is clearly due to other disorders. Among our 70 patients still being followed at five years there are four with recently broken hips, one with hemiplegia due to stroke, and six with moderate to severe dementia (see below).

Is Parkinson's disease progressing in spite of levodopa and other therapy? In a few cases—the development or progression of parkinsonian tremor, rigidity or gait disturbance—the answer is clearly yes. The answer is probably yes in another group of patients who discontinued levodopa and who then got worse than they were before they began taking it several years before. The few patients of Stern et al[65] who became worse than they had been before treatment when switched from levodopa to placebo may fall into this group as well. Thus there is good evidence, in some patients, that there is progression of clinical symptoms in spite of their suppression by levodopa. However, progression of structural changes in the brain is still an open question. It should be recalled there is clinical progression in postencephalitic parkinsonism, even though the presumed virus infection occurred many years before, and the brain at death shows no evidence of progressive disease activity, at least when examined by classical neuropathological techniques.

The optimum daily dosage of levodopa has represented a balance between limiting side effects and producing the best therapeutic effects. Every few months or at the end of a year the dosage was readjusted for each patient. As may be seen in Chart 5 the mean 4.3 gram level at one year (range 1.0 to 9.0 grams) dropped to 3.75 grams

at two years. At that time we anticipated a further drop. However, as may be seen, the five-year level is at 4.1 grams (range 0.75 to 10.0 grams).

Problems in Levodopa Therapy

Problems in the use of levodopa can be listed as follows: progression of symptoms (see above), side effects, potential side effects, treatment failures, development of other central nervous system symptoms, and depression.

The side effects of levodopa are nausea and vomiting, a dyskinesia best characterized as a combination of choreoathetosis and dystonia, the off-on effect, postural hypotension, and organic dementia. Nausea and vomiting may occur with the first oral dosage or as the dosage is being gradually increased; or it may appear only at rather high dosage levels. From 36 to 83 percent of patients may have nausea or vomiting in the induction phase of levodopa therapy.[63,66,67] Approximately 10 percent continue to have these symptoms even after two to four years on levodopa, and may never be able to take their theoretically optimum dosage.[68] In the initial experimental studies with extremely well motivated patients, as few as 1 percent actually stopped taking levodopa because of intractable nausea and vomiting.[63] With less motivated patients who began taking levodopa in the last year of the span covered by this study, possibly 20 percent were sufficiently upset by nausea and vomiting to discontinue the drug before there had been adequate therapeutic trial.

At present the nausea and vomiting are dealt with by having the person take the medication with meals, or take smaller and more frequent doses, or take less medication; and occasionally also by adding a phenothiazine such as prochlorperazine (Compazine®) in low doses. These measures may be satisfactory for many patients, but as indicated in the previous paragraph, these measures are insufficient. Therefore it is gratifying to report that dopa decarboxylase inhibitors which act outside the central nervous system are proving very effective in reducing nausea and vomiting.[66,69,70] Two such inhibitors are Merck's MK-486 (L-alpha methyldopa hydrazine) and Hoffmann-LaRoche's RO 4-4602 (N^1-(DL-seryl)-N^2-(2, 3,4-trihydroxybenyl) hydrazine). These appear to be effective because they allow a pronounced reduction in levodopa dosage and because the site which produces nausea and vomiting is the chemoreceptor zone of the area postrema, which is outside the blood brain barrier.[71] The Hoffmann-LaRoche inhibitor is now available in Europe as Madopar®, a fixed combination tablet with levodopa. The Merck inhibitor should be marketed in late 1974 in the United States, also as a fixed combination tablet with levodopa. Its name will be Sinemet®.

Involuntary movements or dyskinesias are best described as choreoathetoid or dystonic. The head may be pulled to one side or the arm externally rotated and extended. The hand may be flexed at the wrist, the forearm internally rotated, and the fingers extended. The back may twist or the leg rotate. The jaw may be clenched or the eyelids held shut. There may be rather rhythmic contractions of the thoracic or abdominal muscles. If these movements are quite rapid, the term *chorea* applies. If they are slower and have a writhing character, they are *athetoid*. If the disturbance lasts many seconds and is more of a postural disturbance, it is called *dystonia*.

The dyskinesias were observed in the first trials of levodopa at high dosage[58] and have been a problem since then.[66,72,73] In patients who were going to have levodopa-induced choreoathetosis, usually it began in the first three to twelve months of therapy. In some the involuntary movements began when levodopa dosage was first elevated, but in many others it occurred after they had been taking a steady dose for many months. The average dosage at which the choreoathetosis appeared was 4.5 grams daily. Most patients have had it controlled by a drop in dosage of 0.5 to 1.0 grams. In a few cases such a reduction has led to return of significant parkinsonian symptoms, and the patients have had daily fluctuations between parkinsonian akinesia and levodopa-induced choreoathetosis. One problem in regulating such patients is that some would rather have a significant degree of choreoathetosis than parkinsonian akinesia or rigidity. The problem is compounded by the fact that some patients, including those with intact mentation, simply are not aware of how severe the choreoathetosis is.

At the end of the first year of levodopa therapy, 8 of 93 patients were having choreoathetosis, 4 severely. (However, it should be noted that 38 patients had had choreoathetosis some time during the year but most responded to a reduction in medication.) At the end of five years 16 of 70 patients were having choreoathetosis, two severely.

The choreoathetoid movement disorder second-

ary to levodopa is almost entirely restricted to patients who also have parkinsonism. We did not see it in six normal persons who voluntarily took the medication.[74] We have not seen it in many patients with dystonia musculorum deformans or spastic torticollis who have taken sizable doses for many months. It is not seen in manganese poisoning, a variety of parkinsonism whose anatomical substrate is unclear.[75] It may have appeared in a few patients with depression being treated with levodopa, but the descriptions are not adequate for us to decide.[76] However, we and others have seen levodopa accentuate choreoathetosis in Huntington's chorea or be transiently present in certain young adult offspring of a parent with Huntington's chorea who one day may show clinical manifestations of this disease.[77] The bulk of evidence indicates levodopa-induced choreoathetosis rarely appears except in patients with Parkinson's disease or Huntington's chorea.

Another phenomenon should be noted. In the first few days of therapy, the phenothiazines and butyro phenones (haloperidol for example) are likely to produce dystonic spasms of the face, tongue and neck which closely resemble levodopa-induced choreoathetosis. While these drugs are considered to block the receptors of dopamine (and serotonin and norepinephrine), there may be an initial excitatory effect; or their role in increasing the synthesis and release of dopamine may be paramount.[78]

Levodopa-induced choreoathetosis in Parkinson's disease occurs only at massive oral doses or about the level necessary to relieve the parkinsonian symptoms. Further, we have not seen it occur in those few parkinsonian patients who were unresponsive to levodopa. These patients may either have no nigral-striatal cells left[79] or may have significant damage to the globus pallidus, the main outflow path from the striatum.

The above evidence and speculations suggest the following mechanisms for levodopa-induced choreoathetosis. Too much levodopa activity is present at some dopaminergic receptor sites in the striatum. Such receptor sites may get too much levodopa from excessive sprouting of the remaining nigro-striatal terminals (see earlier section on Anatomy and Histochemistry); or from dopamine formation in striatal serotoninergic terminals which may have had aberrant sprouting in the region of the dopamine receptor cells. Still another possibility is that the denervated dopamine receptors may have become hypersensitive on the model of acetylcholine hypersensitivity in sympathetic ganglia. In the case of levodopa-induced choreoathetosis in Huntington's chorea, the loss of some striatal cells which have dopamine receptors could trigger other striatonigral axon sprouting or hypersensitivity. These several hypotheses are now being investigated.

The off-on effect refers to sudden swings between severe parkinsonian symptoms and normal mobility.[66,68] It occurs in parkinsonian patients who have been taking levodopa for a long time, usually one to two years. The akinesia or other symptoms come on in a few minutes, and a patient who was walking briskly about may suddenly find himself immobile. This may occur several times a day, and it may be either predictable or quite unpredictable. In some patients the "off" effect may be precipitated by emotional stress or by exercise. Sometimes it is correlated with the time of taking the levodopa and occurs sooner and sooner after the last oral dosage. In some patients the choreoathetoid side effect may be interposed, so that he swings from parkinsonian symptoms, to no symptoms, to choreoathetosis. At two and a half years, six of 91 patients showed this phenomenon, two severely.[68] At five years, seven of 70 showed it, one severely.

The cause of the off-on effect is unknown, but the basis is almost surely sharp fluctuations of dopamine level in the striatum. Many processes might cause this; more rapid destruction of dopamine within the synaptic ending or in the synaptic cleft seems most likely to us. Or the remaining nigral cells, becoming still fewer as time goes by, are straining to the utmost to make dopamine. This seems not quite as likely, since all those patients at the two-and-a-half-year point who had the off-on effect are still having it, and their overall parkinsonian state has not changed materially. Also to be considered are the many steps from stomach to brain through which the dopa must pass. In this regard neither the peripherally acting dopa decarboxylase inhibitors[69] nor the slowly absorbed forms in the gastrointestinal tract seem to help the off-on effect. (We have had personal experience with one of the latter preparations.)

Postural hypotension induced by levodopa is occasionally troublesome and more often causes worry on the part of the conscientious physician taking the blood pressure readings. We defined postural hypotension as a fall in systolic blood pressure of more than 30 mm of mercury on changing from either the supine or sitting to stand-

ing position It is mainly a problem of the first year of therapy. In 58 patients, evaluated in the first year of therapy,[80] we found no significant changes in supine and standing blood pressure in the group as a whole. However, six of these 58 patients did have pronounced decreases in blood pressure on standing. Heart rates did not change significantly, even when blood pressures were recorded at their lowest. The orthostatic hypotension seemed to parallel the period of maximal improvement in akinesia or rigidity, and was often at a time when the patients were exercising only a little. The postural hypotension in the above six patients caused virtually no symptoms, some patients complaining of feeling "dizzy" only when directly questioned. Other investigators have described actual syncope.[61,66] Since that time we have also had several patients who actually fainted on standing. However, it is generally accepted that postural hypotension is predominantly a problem of early levodopa therapy. In the group of patients comprised in this study, none are having postural hypotension at the five year follow-up.

Postural hypotension may have either a peripheral[81] or central cause, or both. The former is suggested by the relief given by a peripherally acting dopa decarboxylase inhibitor to several patients with symptomatic postural hypotension. The impaired cardiovascular response to postural changes in the old or infirm is a major factor in addition to the more specific one of levodopa. See Markham et al[80] for further discussion.

Treatment of postural hypotension at present consists of using elastic stockings or fludrocortisone acetate (Florinef®) or ephedrine. Lowering the dose of levodopa may help, but it also interferes with the desired increase in mobility. Use of peripherally acting dopa decarboxylase inhibitors (see below) offers the best hope for the future. We are now inclined to treat only those patients who are actually having symptoms from the low blood pressure.

Mental confusion, delirium, euphoria, and other manifestations of an organic or drug-induced confusional state occasionally accompany the use of levodopa. Some patients in our study would lapse into a mute and unresponsive but still conscious state. This was not nearly as frequent or as severe as that accompanying the use of atropine or other anticholinergic drugs, but was the same kind of response. It occurred almost entirely in patients who had pre-existing organic mental changes, some of whom also had parkinsonism of post-encephalitic origin. It is clearly secondary to the use of levodopa, and is clearly related to dose—that is, 3.0 grams of levodopa may produce significant confusion, yet 2.5 grams causes little. In our experience, if a patient had levodopa-induced confusion early in therapy at a given dose, he was very likely to have it even years later when this dose was again reached. In the first year of levodopa therapy, we saw drug-induced confusion in six patients. At the end of five years, these six plus one other had the problem. The main way of dealing with it is to stay below the critical dose, or if it must be given from the standpoint of the parkinsonism, to have a companion with the patient at crucial times.

Hypersexuality secondary to levodopa is a rare phenomenon, but of course attracts much interest. Usually an increase in sexual function follows improvement in general mobility and well-being. However, in one case a somewhat demented 53-year-old man with post-encephalitic parkinsonism became sexually aggressive whenever he was given levodopa. Repeated determinations of follicular stimulating hormone (FSH), luteinizing hormone (LH) and serum testosterone, both while receiving and not receiving levodopa, have been normal. (See also Lundberg.[85]) Possibly related is the report of a twin boy with epilepsy who had penile enlargement (compared with his twin) and became sexually aggressive while receiving levodopa.[86] The precise role of levodopa in the production of hypersexuality is unclear. However, a common thread connecting such cases appears to be organic brain damage.

Potential side effects are two: disturbances from growth hormone elevation, and serious cardiac arrhythmias. Sirtori and coworkers reported transient elevation of human growth hormone (HGH) in patients with parkinsonism two hours after single doses of levodopa given in the course of chronic levodopa therapy.[82] On this basis and also the finding of some impairment of carbohydrate metabolism, these investigators suggested that patients receiving long-term levodopa therapy be carefully watched for the development of acromegaly. However, the 70 patients we have now followed for five years, plus the groups followed by other investigators,[83,84] have shown no clinical signs of acromegaly.

The basal level of HGH was not altered after a year of levodopa therapy[82] and transient HGH elevations have also been noted in deep sleep, after acute hypoglycemia, after exercise and other

stress, and after ingestion of arginine and other amino acids. It is likely the transient elevations of HGH following levodopa fall into this group.

Serious cardiovascular problems secondary to levodopa are best considered potential rather than actual side effects.[81] A few patients in our series have had premature ventricular contractions, and a few more have complained of palpitations but have had normal electrocardiograms. Minor disturbances in cardiac rhythm are common in the age group of patients with parkinsonism, and at least in our series we were not convinced such cardiac irregularities were related to levodopa. However, McDowell et al[73] did have several patients with premature ventricular contractions and one patient each with paroxysmal atrial fibrillation and flutter which they felt may have had some relationship to the levodopa. These patients were treated with diphenylhydantoin (Dilantin®) or procainamide (Pronestyl®) and the levodopa was continued.

Treatment failures consist of several categories of patients:

1. Side effects are so distressing the medication has to be stopped. These have been discussed above.

2. Misdiagnosis. The tremor in patients with essential tremor (also called familial or senile tremor) may be mistaken for that in parkinsonism. However, essential tremor occurs during maintained posture or movement, not when the muscles are relaxed. These patients do not have rigidity, akinesia or some of the hallmarks of Parkinson's disease. Rigidity and postural distortion may be seen in Jakob-Creutzfeld disease, Wilson's hepatolenticular degeneration, and certain other rare basal ganglia diseases. However, the course of these illnesses, plus the "non-parkinsonian" features, usually clarifies the problem.

3. More disturbing are patients who seem to have classical Parkinson's disease but who do not respond to levodopa, or who have a good but transient response. Some of these havc now been shown to have striatonigral degeneration.[13,87,88] Other minimal responders to levodopa with clinical parkinsonism may have other diseases such as massive degeneration of the globus pallidus. However, such cases have not yet been verified at post mortem. In at least some of these patients choreoathetosis does not develop, even with large doses of levodopa.[89]

4. Still another group of non-responders may have bona fide Parkinson's disease but have defective absorption of levodopa from the bowel, eithcr because of high gastric acidity or decreased motility.[90]

As the years go by, new non-parkinsonian symptoms may complicate the patient's life. We shall pass over the obvious such as stroke and cancer. Dystonia, dementia and depression are of particular concern.

Dystonia, or mobile spasm, may occur to a limited part of the body during long-term levodopa therapy. This is not dose-related, does not seem to occur in patients who have levodopa-induced choreoathetosis, may continue even if levodopa is discontinued, and was occasionally seen before levodopa was introduced. Patients with this response in its most modest form complain that the toes of the feet "curl up" or press into the ground or into their shoes. Three of our patients have this as their present main complaint. In one patient dystonic rigidity of both legs and feet has slowly developed. Parkinsonian symptoms are under good control with levodopa. Since dystonic symptoms frequently occur in the post-encephalitic state, possibly it should not surprise us to find something like it occurring in patients with prolonged survival because of levodopa.

Organic dementia refers to the changes in intellect and judgment from some damage or defect in the brain. "Normal" alterations with age have to be considered. At its most subtle, it might consist of minor errors in judgment so that only a man's long time business associates begin to wonder. Such persons coming into the hands of neurologists and psychologists are usually considered unimpaired intellectually. With more severe involvement, the neurologist can usually detect abnormalities during the history-taking, questions reflecting orientation and judgment, immediate and remote recall of names and numbers, repeating numbers forward and backward, repeating a story, and the like. These are all parts of formal intelligence tests, the Wechsler Adult Intelligence Scale (WAIS) being the best known and standardized. When our 93 patients were initially examined before the levodopa trial, we concluded 18 had mild dementia and six had severe dementia, for a total of 26 percent. (See Chart 6.) Formal testing using the WAIS and other tests on a subgroup of 29 patients showed mild but definite intellectual impairment compared with age-matched controls.[91] Such intellectual impairment is independent of depression.[92]

In the first six months of levodopa therapy, there was a modest improvement in intermediate

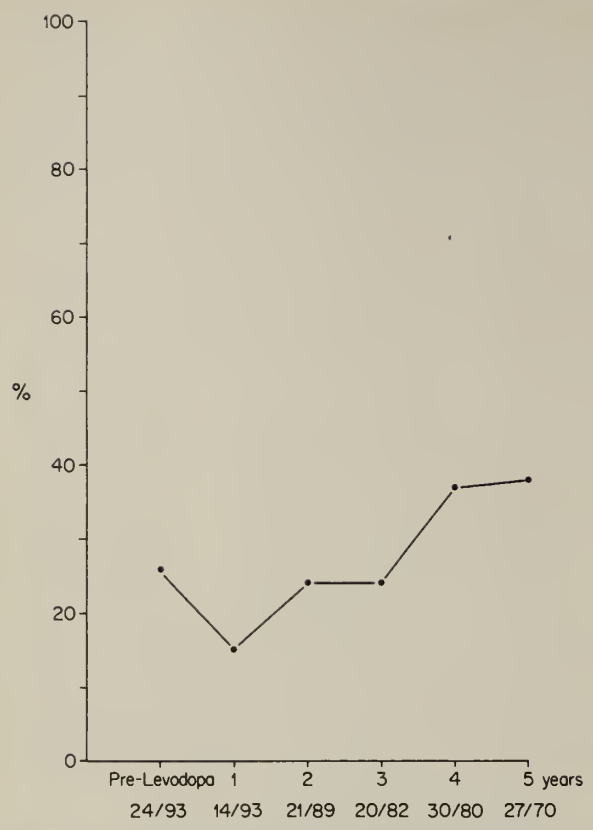

Chart 6.—Percentage of patients with dementia. Twenty-four of 93 patients (26 percent) had dementia before levodopa therapy. At end of five years 27 of 70 patients (38 percent) were demented.

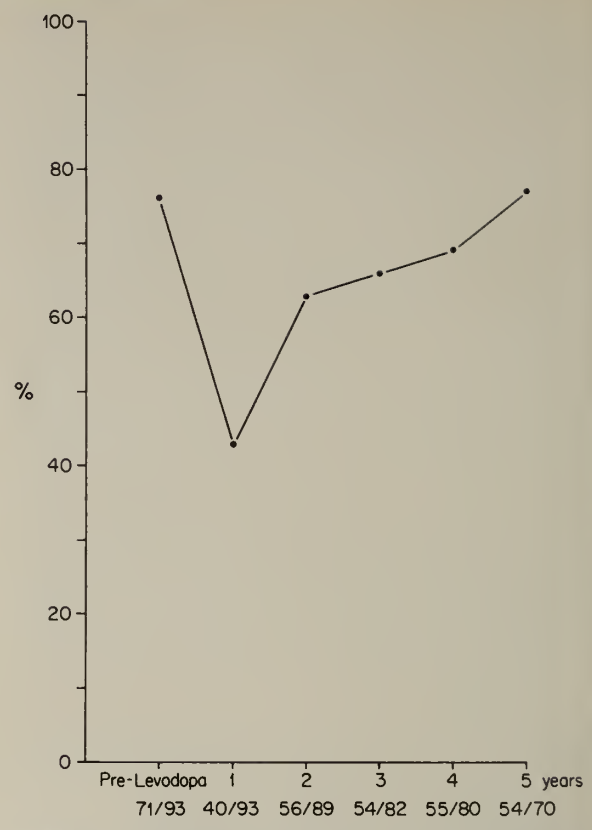

Chart 7.—Percentage of patients with depression. Seventy-one of 93 patients (76 percent) were depressed before levodopa therapy began. After five years of levodopa, 54 of 70 patients (77 percent) were depressed.

memory (verbal learning tests) but not short-term memory.[91] In this study anticholinergic medications, known to cause organic confusion, were kept constant. Another study[93] with changes in anticholinergic medications from the pre-levodopa to levodopa period showed a more significant improvement in intellectual functioning.

As more time passed, it became clear that dementia was increasing in those who initially had impairment, and was developing in others. This occurred with nearly constant individual doses of levodopa, and any effect from anticholinergic medications was vitiated by discontinuing such medications. After five years of receiving levodopa, 10 of 70 patients had severe dementia and 17 had mild dementia, for a total of 38 percent. In addition, two others of our original group were no longer receiving levodopa; they were in nursing homes because of severe dementia. Thus we must conclude organic dementia is a very common accompaniment of Parkinson's disease.

Depression is also very commonly found with Parkinson's disease. It was present in 76 percent of the patients in the present series before levodopa began, and has been reported to be present in almost 90 percent of another series.[94] It may be identified by the patient's description of feelings of hopelessness, worthlessness and lassitude. Self-depreciation may be expressed in other ways, including somatic complaints, some of which are difficult to separate from those due to Parkinson's disease per se. Tension, anxiety and guilt are expressed in the same ways as in non-parkinsonism patients. The only caution is that signs such as inexpressive face, flexed posture, and slow movement may be seen in Parkinson's disease alone, and are not reliable guides to the presence of depression.

Our initial data on 93 patients indicated 76 percent were depressed. Some had become depressed after the onset of Parkinson's disease, while others were clearly depressed years before. Other investigators also have observed pre-existing depression.[95] There was no apparent correlation

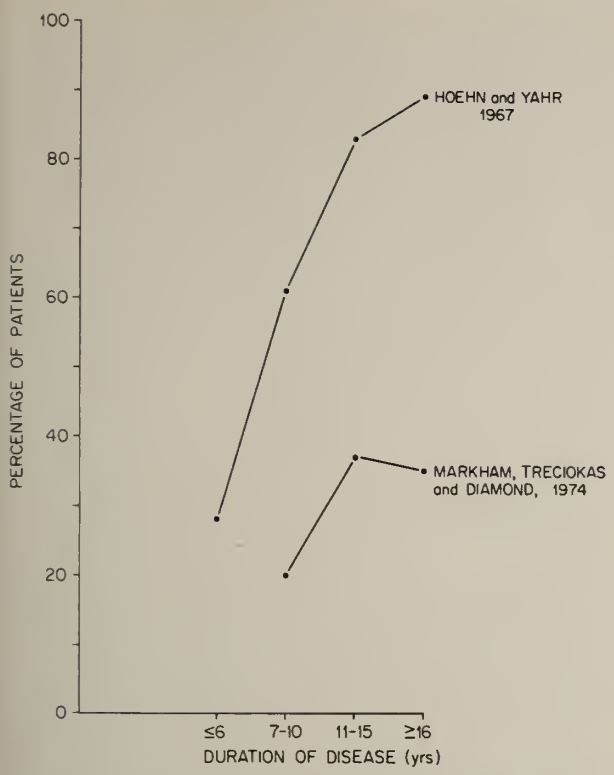

Chart 8.—Serious disability and death with primary parkinsonism. In Hoehn and Yahr's series[1] patients in Stages IV or V or dead ranged from 28.1 percent at duration of 6 or fewer years to 89.5 percent at duration of 16 or more years. In present series, 20.0 percent were in Stages IV, V or dead after 7 to 10 years; 34.7 percent after 16 or more years.

between depression and the stage or duration of Parkinson's disease, or age.

After patients had been receiving levodopa for a year, our clinical assessment was that the proportion who were depressed had fallen to 43 percent. Most of the patients had significant improvement in their parkinsonian symptoms, but we could make no correlation between degree or manner of improvement and the changes, if any, in the depression. However, an analysis of depression using the Minnesota Multiphasic Personality Inventory (MMPI) at six months[93] and at 15 months[96] showed no significant change from the pre-levodopa scores. These results appear to conflict, but it is difficult to compare an objective, sharply focused test with a broader, more subjective evaluation. In any case, it is clear that by the second year and thereafter the depression is unchanged from the pre-levodopa period by either system of measurement.

It has been suggested that levodopa aggravated depression in about 12 percent of cases,[66] but a more direct assessment of this point seems to indicate levodopa neither helps nor worsens depression.[76] Our experience fits with the latter view.

Whether depression in Parkinson's disease is endogenous or reactive (to the disease or other aspects of the patient's outward life) is not clear. However, the facts that it may precede the onset of parkinsonism in some cases (see above), and is not significantly altered by often major physical improvement, suggest the depression is the endogenous type.

Treatment of the depression with tricyclic antidepressants, such as amitriptyline (Elavil®), protriptyline (Vivactil®), or imipramine (Tofranil®), has usually been adequate. However, three patients, under our observation but not in the present series, had electroshock therapy with prompt and excellent relief from depression. In two of these three patients there was also a pronounced improvement in motor function even though levodopa and other anti-parkinsonian medications were held constant.

Morbidity, Progression and Mortality

Extent of disability and death. In an effort to evaluate the long term effects of levodopa on morbidity, progression and mortality in Parkinson's disease, the study of Hoehn and Yahr[1] has been useful in providing a carefully delineated baseline for these processes as they were observed before levodopa became available. Hoehn and Yahr studied 856 patients bearing the diagnostic labels of paralysis agitans, Parkinson's disease, or parkinsonism, between the years of 1949 and 1964 inclusive. Although their study is largely a cross-sectional approach, and ours a longitudinal, several direct comparisons may be made.

The progression of disability in primary parkinsonism (paralysis agitans) is reported by Hoehn and Yahr in their Table 5. Patients who died or were in Stages IV or V (severely disabled) were described in terms of "year of first observation" to 1964. These investigators state that average duration of illness was one year longer than the period of observation, hence duration of disease may be computed. Percent of patients dead or seriously disabled in Hoehn and Yahr's group progressed from 28.1 percent of those with disease duration of six or fewer years, to 61 percent of those with duration of 7 to 10 years, and finally to 89.5 percent of those with duration of 16 or more years. Our group showed 20.0 percent dead or disabled after disease duration of 7 to 10 years,

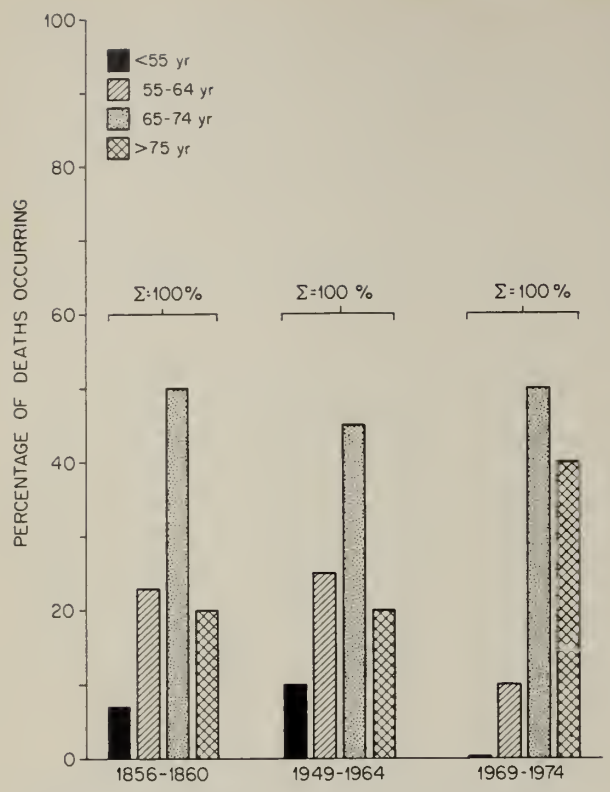

Chart 9.—Distribution of age at death in Parkinson's disease. Before levodopa therapy was available, age at death profiles remained unchanged over the last century, with 30 to 35 percent of patients dead before the age of 65. In the present series, 10 percent died before the age of 65.

rising to 34.7 percent after 16 or more years. (Our study did not include patients with duration less than seven years.) Chart 8 is a graphic depiction of Hoehn and Yahr's Table 5 to facilitate comparison with the post-levodopa progression observed in our patients.

Age at death. Hoehn and Yahr reported 293 deaths among their 672 primary parkinsonism patients, with a mean age at death of 67.0 years. Deaths in our group of 81 with primary parkinsonism numbered 10, with mean age at death 73.5 years. A more detailed analysis of age at death is offered in Hoehn and Yahr's Figure 3, in which they compare the distribution of ages at death of their patients with statistics obtained from the Registrar General's Reports of England and Wales for the years 1856 to 1860. Hoehn and Yahr, in the pre-levodopa year of 1967, state: "A sobering and discouraging fact [is that] despite the addition of a variety of therapeutic measures for parkinsonism over these years, including numerous drugs, surgical procedures, and improved supportive care, the distribution of ages at death has remained essentially unchanged." Chart 9 is a comparison based on Hoehn and Yahr's Figure 3. As they have stated, the distribution profiles of age at death differ hardly at all in the century separating the first two sets. If anything, the 1949-1964 group shows more deaths in the under-55 and 55-to-64 age categories than does the 1856-1860 group. While the number of deaths in our post-levodopa group is small (10 compared to Hoehn and Yahr's 293), it is interesting to note that the profile differs considerably from the previous two. No deaths occurred in the under-55 category, one (10 percent) in the 55-to-64, five (50 percent) in the 65-to-74, and four (40 percent) in the 75 and older category. It is ironic to have to say that we did not observe enough deaths to enable us to make a conclusive statistical statement.

Mortality in primary parkinsonism. In our group of 81 patients with paralysis agitans, the ten deaths were due to the following causes: three aspiration pneumonia, two acute myocardial infarctions, two complications of hip fractures, one complication of a stroke, one cancer of the colon, and one cause unknown. (In our post-encephalitic group of 11 patients, one died of probable barbiturate overdose.)

Hoehn and Yahr conclude that "there would seem to be little doubt that the state of 'parkinsonism' as an entity severely limits life expectancy." Their Table 9 summarizes 241 case of primary parkinsonism seen within two years of onset of the disease, and in which 91 deaths were observed. Calculating the expected deaths from U.S. Life Tables,[97] they find a ratio of observed to expected of 2.9—that is, a mortality rate almost three times that of the general population of the same age. Using the same tables we have subjected our data to the same analysis.

The manner in which expectancy of death was calculated may be seen in Table 1. Each patient was placed in the appropriate five-year category based on his age at entry into the study in 1969. For example, if a patient was 56, he was placed in the 55-to-64 age group. The midpoint of that category was adopted as the age for all patients falling into that range, that is, 57. Then expectancy of death for the five years following that age was computed from the U.S. Life Tables[97]—that is, for ages 57 to 61 inclusive. This rate was then multiplied by the number of patients in that category to determine the number of deaths expected during the five-year interval for that age group.

TABLE 1.—*Expected deaths. Each patient was placed in a five-year category based on his age at beginning of study. Midpoint of category was adopted as age for all in that class. Then the expected death rate for the five years beyond that mid-point was calculated for each category from U.S. Life Tables*[97] *and was multiplied by number of patients within that class to determine the expected number of deaths.*

Expected death rate for age range:	42→46 = .0217	47→51 = .0348	52→56 = .0531	57→61 = .0786	62→66 = .1163	67→71 = .1673	72→76 = .2415	77→81 = .3563
N=	2	3	4	13	17	20	16	6
Expected deaths:	.0217 x 2 = .04	.0348 x 3 = .10	.0531 x 4 = .21	.0786 x 13 = 1.02	.1163 x 17 = 1.97	.1673 x 20 = 3.34	.2415 x 16 = 3.86	.3563 x 6 = 2.13
40 41 42 43 44	SH RM							
45 46 47 48 49		MS JC KG						
50 51 52 53 54			RT PW LO LJ					
55 56 57 58 59				MH LK HS EB ED HB SB SG				
60 61 62 63 64					JS HC JW JP HP "K" JO MJ WF KH ET MO JZ AM JB			
65 66 67 68 69						CT TB MF OG GS DW MM JM WP GK SR HJ TR		
70 71 72 73 74							EH AA MZ OH EO CF NB BW MC	
75+ Years								GB AH LB MB LR KS

AGE AT BEGINNING OF LEVODOPA THERAPY

Table 2 shows observed and expected mortality in 81 patients with primary parkinsonism over the five-year interval from 1969 to 1974. The total deaths observed during that period was 10, the number expected was 12.67; the ratio was 0.7893 to 1—that is, less than expected for the general population. Again, we caution that a group of 10 is a small one upon which to base conclusions. Also other workers have found death rates which differ from Hoehn and Yahr's. Kurland,[98] for example, found a ratio of 1.41 to 1.

TABLE 2.—*Mortality in primary parkinsonism. Expected mortality in group this size and age drawn from general population is 12.67.*[97] *Mortality observed was 10, giving a ratio of observed to expected of 0.7893 to 1. Pre-levodopa study of Hoehn and Yahr*[1] *found a ratio of 2.9 to 1.*

Age at Beginning of Study	*Number*	*Deaths During 5-Year Interval*	
		Observed	*Expected*
40-44	2	0	.04
45-49	3	0	.10
50-54	4	0	.21
55-59	13	1	1.02
60-64	17	0	1.97
65-69	20	3	3.34
70-74	16	4	3.86
75+	6	2	2.13
TOTAL	81	10	12.67

.7893
Ratio of observed to expected

Other Therapy

Drugs other than levodopa still have a place in the treatment of Parkinson's disease. Anticholinergic medications such as trihexyphenidyl (Artane®), benztropine (Cogentin®), procyclidine (Kemadrin®) and several others are still being used in 32 of the 70 patients (46 percent) who have been receiving levodopa for five years. With these patients we have repeatedly tried to discontinue or decrease these medications over the years. However, when they were withdrawn a worsening of rigidity, akinesia, or often tremor indicated these medications were still helping. Returning to the considerations early in this paper, diminished dopamine and a relative (or possibly absolute) increase in Ach are likely. Further, chronic (but not acute) levodopa administration itself causes a small but significant increase in brain Ach concentration in rats.[99] While this needs confirmation and explanation, it may explain the need for anticholinergic drugs along with levodopa.

Amantadine hydrochloride (Symmetrel®) is another useful drug, usually as an adjunct to levodopa. We have one patient who is better with Symmetrel and an anticholinergic drug than he was with levodopa.

Stereotaxic surgical operation for the relief of parkinsonian symptoms was almost abandoned for the first year or two after levodopa became available. Well placed freezing or electrolytic lesions in the ventrolateral nucleus of the thalamus or immediately adjacent areas were very effective in relieving parkinsonian tremor and rigidity in the contralateral side of the body. However, such lesions did not arrest the progression of akinesia, and occasionally produced new neurological disabilities. Speech and intellectual disturbances were not uncommon after a second procedure to deal with the parkinsonism symptoms on the other side of the body. However, as it became apparent that levodopa did not benefit all the symptoms in all of the cases of parkinsonism, interest in stereotaxic operations has returned.

There are two main circumstances in which stereotaxic operations might be considered. Tremor which does not respond to levodopa and other

drugs may be helped by a single stereotaxic lesion. If the tremor is bilateral it may be difficult to decide which side to operate on, for nowadays we would not consider bilateral operations. In the present series, one patient with unilateral tremor which was unresponsive to levodopa had excellent results from cryogenic thalamotomy; as long as he still continues to take levodopa for akinesia he is nearly symptom-free.

The other, rarer, circumstance in which stereotaxic operation might be considered is predominantly one-sided parkinsonian symptoms in a patient who also has severe levodopa-induced choreoathetosis when he takes enough levodopa to help the parkinsonian symptoms. One such patient in the present series had good surgical results for the parkinsonian rigidity and tremor on one side. On about half the previous dose of levodopa, the remaining parkinsonian symptoms are well controlled and he does not have choreoathetoid side effects. Our neurosurgical colleague, Dr. Robert W. Rand, has done stereotaxic thalamotomy on about 15 parkinsonism patients in the last two years, mostly for levodopa-resistant tremor.

New approaches to the treatment of Parkinson's disease, at least for the next few years, revolve around levodopa. Extracerebral dopa decarboxylase inhibitors act in the stomach, liver and brain capillary endothelium[100] to lower the amount of dopa needed. They also considerably reduce the severity and incidence of nausea, vomiting, and postural hypotension. (See the discussion above under side effects of nausea and vomiting.) We have also found a mild but measurable improvement in parkinsonian symptoms themselves in patients who had been receiving levodopa regularly for some years.[69]

Sustained release of levodopa from the stomach or small bowel is one possibility.[101,102] Another is administering drugs which increase the speed of gastric and intestinal motility.[103]

Prevention of dopa transamination in the liver may be useful. Another approach is to preferentially enhance dopamine or possibly dopa motility across the blood brain barrier by attaching a labile lipophilic molecule to it.[104] Even more exciting is the possibility of tailoring dopamine molecules in such a way that they go directly to striatal receptors, not elsewhere in the body, without having to go via the striatonigral neurons.

Finally, it should be stressed the real cure to Parkinson's disease lies in a different direction. It is finding out why cells in the substantia nigra die, and preventing this. This involves a better understanding of the processes of aging, of the failure of enzyme systems and of the buildup and breakdown of metabolic by-products. We anticipate having some of these questions answered in the next decade.

Summary

Levodopa is a most effective but rather difficult therapeutic agent in the treatment of Parkinson's disease. After five years some patients are showing progression of some parkinsonian symptoms. However, our group of patients as a whole is still having fewer parkinsonian symptoms and related disabilities than five years before.

Parkinson's disease is almost invariably progressive and no previous treatment, except in rare individual cases, has altered this course. Before levodopa became available, almost 90 percent of patients with primary parkinsonism (paralysis agitans) were either dead or seriously disabled after 16 years, and in the mature adult years it increased the chances of dying nearly threefold. In the present study, levodopa therapy for five years in adequate doses in patients with primary parkinsonism has been accompanied by a dramatic decrease—to 35 percent—in the proportion of patients in the category of dead or seriously disabled after 16 years; and it appears to have increased life expectancy to normal range.

In certain cases patients with Parkinson's disease have had only modest or transient response to levodopa; most of these appear to have one or more different pathological substrates and necessitate a redefinition of the parkinsonian syndrome. The high incidence of organic dementia and depression also requires a redefinition of the underlying processes in Parkinson's disease.

While levodopa has also opened up many new approaches to basal ganglia physiology and pharmacology, it does not appear to be leading to the ultimate solution of Parkinson's disease. Other approaches are necessary to determine why the large pigmented cells in the substantia nigra, and certain other cells in the central nervous system, die prematurely.

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Refer to : Yoshikawa TT, Goodman SJ: Brain Abscess—Teaching Conference, University of California, Los Angeles, and Harbor General Hospital, Torrance (Specialty Conference). West J Med 121:207-219, Sep 1974

Specialty Conference

Moderator

THOMAS T. YOSHIKAWA, MD

Discussants

STANLEY J. GOODMAN, MD
THOMAS T. YOSHIKAWA, MD

This is a transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. These conferences have been edited by Doctors Jerrold A. Turner, John Z. Montgomerie, Anthony W. Chow, Thomas T. Yoshikawa and Lucien B. Guze.

Brain Abscess

THOMAS T. YOSHIKAWA, MD:* Treatment of brain abscesses, unlike treatment of most infected purulent material, has failed to achieve the high rate of cure usually resulting from traditional therapy with antibiotics and surgical drainage. Although this infection does involve a vital organ that is not easily accessible, the failure to improve the survival rate in the past two or three decades must be due in part to inadequate recognition and management by practicing physicians. Thus, in this symposium, the clinical recognition and management of brain abscess will be emphasized. Dr. Stanley Goodman will begin the discussion by stressing some key aspects of clinical recognition of brain abscess and the approach to diagnostic evaluation of this disease. I will review the microbial flora of brain abscess and the proper approach to antibiotic therapy. Dr. Goodman will conclude by commenting on the neurosurgical therapy of this disease.

From Divisions of Infectious Diseases and Neurosurgery, and Department of Surgery, University of California, Los Angeles, School of Medicine, Harbor General Hospital, Torrance.

*Fellow, Division of Infectious Diseases, Harbor General Hospital.

Reprint requests to: Division of Infectious Diseases, Department of Medicine, Harbor General Hospital, 1000 West Carson Street, Torrance, CA 90509.

Clinical Diagnosis

STANLEY J. GOODMAN, MD:† It is appropriate that a review of the subject of brain abscess begin with comments on diagnosis. With the development of potent antimicrobial therapy, the mortality rate from brain abscess declined from virtually 100 percent to 40 percent. However, over the past thirty or so years, there has been no further improvement in the mortality rate.[1] Some of the patients who die from brain abscess have overwhelming disease, such as huge necrotic lesions, "malignant" cerebral edema, multiple abscesses, rapid progression of one or more cerebral herniation syndromes, deficiency in host defense mechanisms or severe underlying diseases. Yet there are many patients who die from brain abscess with a clinical course that was "benign" for awhile but ultimately fatal. My contention is that fully one-half of the brain abscess deaths occur in this "benign" and, therefore, potentially salvageable category, and that correctable physician-related problems contribute to the lethality of these otherwise curable lesions. There are several recurring

†Chief, Division of Neurosurgery, Harbor General Hospital; Assistant Professor of Surgery, UCLA School of Medicine.

physician-related problems: (1) when the diagnosis is incorrect or not considered; (2) when inappropriate and highly dangerous diagnostic studies are done; (3) when the diagnosis may have been made but there is tardiness in instituting therapy, overlooking the fact that these lesions may progress with extraordinary speed and (4) when surgical therapy is appropriately instituted but the entire abscess is missed by the exploring needle, or the extent of the loculations is not adequately appreciated. Since the successful management of a patient with a brain abscess often depends on early clinical suspicion, my comments will be directed to the clinical setting that should trigger suspicion.

The "Composite Symptoms" Approach

Any attempt to describe a typical brain abscess patient would not produce a very exact picture. Yet virtually every article dealing with the subject of brain abscess that does describe symptoms and signs simply lists those clinical features encountered, in order of frequency. The symptoms and signs are nonspecific and it is difficult to extract the information needed for increased clinical suspicion. I propose that patients with brain abscesses present basically in one of several recognizable syndromes, and although these syndromes are not specific for abscess alone, they are helpful to keep in mind because these syndromes emphasize the ominous and precarious nature of the intracranial mass dynamics. Before describing these four syndromes, we should review the reasons why brain abscesses present so bewildering an array of symptoms and signs.

Variation in Clinical Symptoms and Signs

The host-organism interaction may be so indolent as to cause a slowly emerging, focal dystrophic calcification within the brain. Conversely, this interaction may be so fulminant as to cause only a small nidus of "infection" but with an enormous surrounding edematous brain tissue response. The edematous brain, confined within the rigid skull, then becomes the lethal component causing increased intracranial pressure, decreased cerebral blood flow and herniation. Or, the host-organism interaction may provoke a thick-walled, collagenous capsule that in itself becomes important because of its tumorous size.

Brain abscesses may be unicentric or multifocal. The vast majority (90 percent) of abscesses resulting from pericranial infection (sinusitis, mastoiditis, otitis media) are unicentric, but many of the hematogenous-borne brain abscesses (for example, those from bacterial endocarditis, pulmonary infection and osteomyelitis) are multifocal, especially in patients with cyanotic congenital heart disease.[2]

Obviously, some clinical symptoms or signs result from the particular location of the abscess or abscesses in the brain. A pontine abscess will cause specific brain stem symptoms and signs, distinguishable from an abscess in the occipital lobe. What is less obvious but of crucial importance in successfully managing these patients is the array of "neighborhood" complications that can arise. The pontine abscess can bulge posteriorly, block the aqueduct of Sylvius acutely at some time, and cause obstructive hydrocephalus requiring urgent surgical venting of the ventricular system. The occipital lobe abscess could rupture, or leak, into the ventricular system, causing life-threatening ventriculitis (or ependymitis) and perhaps necessitating intraventricular chemotherapy or ventricular drainage or more direct and rapid abscess drainage. Or the occipital lobe abscess could involve the transverse sinus, causing a spreading thrombophlebitis and necessitating very attentive treatment of the associated cerebral edema and seizures.

Many other subtleties could be discussed regarding varied pathophysiological features. However, in general, the clinical syndrome will be caused by the forces involved in the host-organism interaction, the number and size and distribution of abscess, the specific brain structures involved and the "neighborhood" anatomy disturbances involving cisterns, ventricles, dural venous sinuses and the like.

Brain Abscess: Four Basic Clinical Syndromes

Since brain abscesses cause damage by altering intracranial mass dynamics or by destroying the brain in a necrotizing fashion, four syndromes have been formulated that depict most of the clinical features of patients with such lesions. A review of charts from 24 patients with proven brain abscess (Table 1) treated in the past ten years at UCLA Medical Center (10 patients), Harbor General Hospital (5 patients) or the Wadsworth Veterans Hospital (9 patients) serves to emphasize four distinct syndromes of brain abscess and to place in clearer perspective problems in disease recognition and in adequate surgical management.

TABLE 1.—*Data on Patients with Brain Abscess Classified by Four Types of Clinical Syndromes*

Patient	Age (years)	Abscess Location	Initial Suspected Diagnosis	Outcome	Cause of Death	Worsened by LP?	Origin of Infection, Predisposing Factor, Underlying Disease	Organism from Abscess	Antibiotic Therapy	Surgical Therapy
TYPE I: RAPID FOCAL MASS EXPANSION										
1	10	Brain stem	Brain abscess	Died	Inc. abscess drainage	No	Cyanotic congenital heart disease	Peptostreptococcus	Multiple	Suboccipital craniectomy; aspiration*
2	35	Right frontal	Brain abscess	Survived; residual seizures	..	No	Putrid pneumonia	Bacteroides	Penicillin	Burr hole; aspiration*; catheter in place
3	47	Left temporo-parietal	Metastatic Ca	Survived; residual dysphasia	..	Probably	Bronchiectasis; pneumonia	Fusobacterium fusiforme	Chloramphenicol, Lincomycin	Burr hole; aspiration*
4	59	Right frontal left parietal	Metastatic Ca	Died; CNS function improving	G.I. bleeding	No	Bronchitis, empyema	Anaerobic streptococci	Penicillin	Burr hole; aspiration; right frontal and left parietal craniotomy; excision
5	1½	Right fronto-parietal	Brain abscess	Survived; no residual	..	No	Cyanotic congenital heart disease	Bacteroides fragilis Anaerobic streptococci	Methicillin, Chloramphenicol	Burr hole; aspiration
6	26	Right thalamus	Intracerebral hematoma	Died	Sepsis w/bleeding into abscess cavity	Possibly	Pneumonia; cirrhosis; steroid therapy; ?DIC	"Hemophilus-like" organism	Penicillin, Cephalothin	Stereotaxic biopsy; aspiration*
7	45	Left temporal	Brain abscess	Survived; no residual	..	No	Chronic otitis media	Paracolon species	Multiple	Burr hole; aspiration*; catheter in place
8	34	Right temporal	Brain abscess	Survived; no residual	..	No	Chronic otitis media	Anaerobes not fully characterized	Penicillin	Burr hole; aspiration
9	6	Right temporal parietal	Brain abscess	Died	Cerebral edema	Probably	Cyanotic congenital heart disease	Sterile culture	Chloramphenicol, Cephalothin	Burr hole; drainage
10	35	Left parietal	Glioma vs. hematoma	Survived; no residual	..	Yes, major herniation	None found	Microaerophilic streptococci	Penicillin, Chloramphenicol	Craniotomy; drainage; re-aspiration
TYPE II: INTRACRANIAL HYPERTENSION										
11	47	Right frontal	Meningitis	Survived; severe neurological deficit	..	Possibly	Post-op craniotomy	Sterile culture; CSF with Gram (+) cocci on smear	Methicillin, Penicillin, Gentamicin	Burr hole; drainage
12	33	Left temporal	CNS disease of unknown etiology	Died	Rapid herniation 6 hours post admission	LP not done	Severe chronic gingival infections	Culture report lost	None. Died before Rx started	None. Advanced too rapidly; Angiogram—"carotid-stop"
13	38	Left occipital	?Migraine ?glioma ?meningitis	Died	Herniation 2° LP and missed abscess	Yes, major herniation	None found	E. coli	Multiple	Burr hole; aspiration
14	20	Left frontal	Brain abscess	Survived; no residual	..	LP not done	Prior gun shot wound to head	Hemophilus sp.	Ampicillin, Cephalothin	Burr hole; drainage; craniotomy with total excision
15	34	Right frontal	Brain abscess	Survived; no residual	..	LP not done	Pansinusitis	Microaerophilic streptococci	Penicillin	Burr hole; aspiration; frontal sinus drainage
16	39	Right cerebellar hemisphere	Brain abscess	Survived; no residual	..	No	Chronic mastoiditis	Proteus sp.	Ampicillin, Chloramphenicol	Burr hole; drainage
17	21	Left temporal	Brain abscess	Survived; no residual	..	No	Chronic mastoiditis	Proteus sp.	Ampicillin, Chloramphenicol, Methicillin	Burr hole; drainage
18	15	Right occipital	Brain abscess	Survived; no residual	..	No	SBE; rheumatic mitral stenosis	Staphylococcus aureus	Nafcillin, Dicloxacillin	Craniectomy; catheter drainage*
TYPE III: DIFFUSE DESTRUCTION										
19	34	Diffuse left hemisphere	Brain abscess	Died	Sepsis; cerebritis	No	SLE; septic arthritis; sepsis; steroids	Culture sterile; Gram (−) rod on smear in brain, blood, joint	Cephalothin	Stereotaxic biopsy; minimal fluid; no drainage
20	48	Diffuse bilateral	Brain abscess	Died	Diffuse cerebritis	No	Not found	Nocardia sp.	Multiple	Burr hole; aspiration
21	54	Diffuse, brain and meninges	Brain abscess	Died	Diffuse cerebritis	No	Not found	Actinomyces sp.	Penicillin, Chloramphenicol	None. Clinically and angiographically failed to "localize" lesion
TYPE IV: FOCAL NEUROLOGICAL DEFICIT										
22	61	Right occipital	Glioma vs. meningioma	Survived; no residual	..	Yes	Acute diverticulitis with prolonged fever	Beta streptococci	Penicillin	Burr hole; aspiration*; craniotomy with total excision
23	43	Left paresagittal parietal	Meningioma	Survived; no residual	..	No	Not found	Cryptococcal granuloma	Amphotericin B	Craniotomy with total excision
24	38	Left parietal	Glioma vs. meningioma	Survived; residual seizure	..	No	Old skull fracture; bone fragment in abscess	Staphylococcus aureus	Penicillin, Methicillin	Craniotomy with total excision

*Antibiotic irrigation into abscess cavity either at time of surgery and/or postoperatively.

Abbreviations LP = lumbar puncture Inc = incomplete CNS = central nervous system Ca = carcinoma DIC = disseminated intravascular coagulation CSF = cerebrospinal fluid SBE = subacute bacterial endocarditis SLE = systemic lupus erythematosus

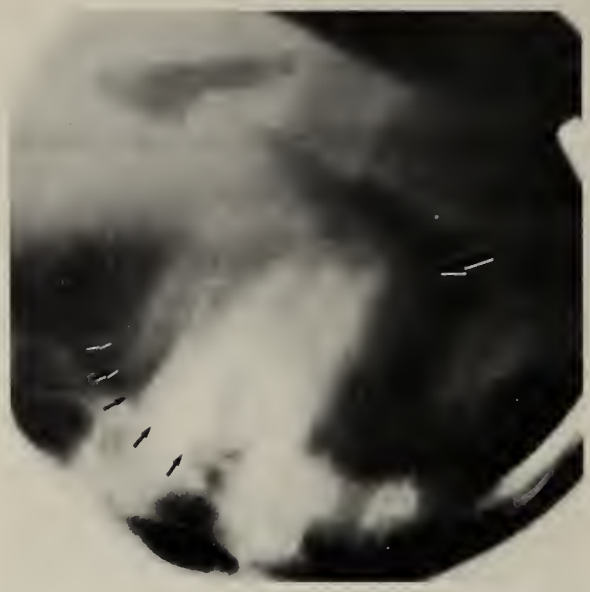

Figure 1.—Midline lateral tomographic view during pneumoencephalogram. Small arrows outline anterior border of pons against the clivus. Large arrow points to posterior aspect of abscess bulging into fourth ventricle.

These four syndromes undoubtedly do not depict all varieties of brain abscess presentation, but abstracting syndromes from clinical data may help physicians recognize disease processes earlier.

Type I abscess presentation (rapid focal mass expansion). Ten patients presented with the symptoms and signs of a rapidly progressive localized intracranial mass lesion. The rapidity of the neurologic progression was usually days to weeks, but in two instances the progression was over hours. Therefore, in terms of the temporal profile, these lesions behaved like malignant astrocytomas, metastatic neoplastic tumors or even spontaneous intracerebral hematomas. Localization to the correct lobe of the cerebral hemispheres, cerebellum or brain stem in the posterior fossa on clinical criteria alone was possible and usually accurate.

In this group, a correct clinical diagnosis was made early in six of the ten patients because of associated known facts (three children with cyanotic congenital heart disease, two adults with chronic otitis media and purulent drainage and one adult with recent cavitating bacterial pneumonia). Despite the fact that these patients presented with a rapidly expanding mass syndrome, there was at least one lumbar puncture (LP) done on each patient in this group: one patient had a major uncal herniation syndrome 40 minutes after the first LP; one patient had accelerated neurological deterioration over three days coinciding with three daily LP's and one patient's hemiparesis worsened about three hours after an LP. Three patients died from complications related to the abscess.

One death occurred, in a ten-year-old with a brain stem abscess. This lesion was correctly diagnosed clinically, was subsequently localized with both pneumoencephalography and cerebral angiography (Figure 1) and was partially drained following surgical exploration of the posterior fossa (Figure 2). The patient showed significant and sustained neurologic improvement for two weeks, then rapidly deteriorated over a 24-hour period and died while plans were being made to return her to the operating room. On autopsy, large loculations of abscess more rostral in the brain stem that had not been drained by the first procedure were observed (Figure 3). Another example of a Type I lesion is described in the following case.

REPORT OF A CASE

A 35-year-old man, a heavy smoker, was admitted to hospital because of a three-week cough productive of thick, foul-smelling sputum and chest wall pain. Lobar and hilar infiltrates were seen on chest x-ray films. Soon after admission, a right hemiparesis, progressive dysphasia and right homonymous hemianopsia rapidly developed and, eventually, there were seizures and papilledema. The clinical suspicion was that the patient had a malignant pulmonary lesion with secondary pulmonary infection and brain metastasis. A positive brain scan and a cerebral angiogram showing a large avascular lesion were interpreted as supporting the original clinical diagnosis. Finally, after repeat cytological examinations of sputa failed to show malignant cells, and after bronchoscopic biopsy yielded only "inflammatory changes," burr hole exploration and abscess aspiration were done. Preoperatively, the patient was given penicillin G intravenously, 20 million units a day, and this was continued following operation. This patient had deteriorated during a period of three consecutive LP's. The patient made a good recovery except for mild dysphasia.

Type II abscess presentation (intracranial hypertension). Eight patients presented with symptoms and signs predominantly of neurological deterioration associated with intracranial hypertension. These patients complained of headache, nau-

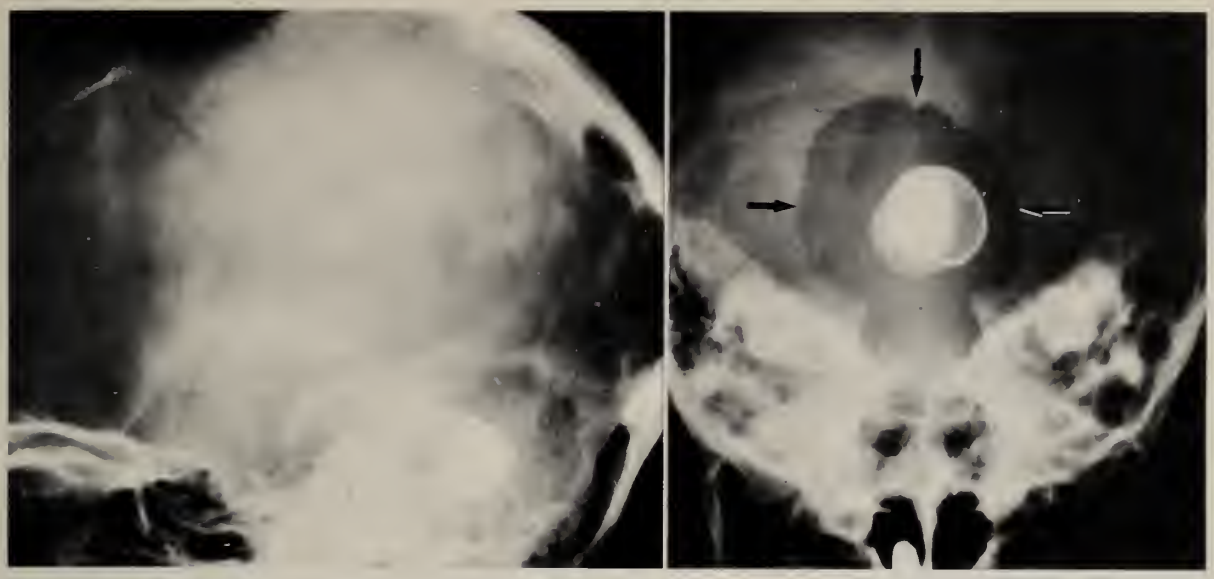

Figure 2.—Left, lateral plain skull x-ray film. Contrast material has been absorbed by cells lining the abscess cavity, therefore, contrast material outlines the size and shape of the abscess cavity on plain x-ray film. **Right,** Towne view plain x-ray film. Arrows point to margins of bone opening (suboccipital craniectomy) used for direct approach to abscess cavity in brain stem.

Figure 3.—Brain specimen obtained at autopsy. View of multiloculated abscess within the upper brain stem. Arrows point to thick-walled collagenous capsule surrounding contiguous abscess cavities.

sea, vomiting, obtundation, memory loss or some other defect in mental function and personality change. Papilledema was a commonly encountered sign. Some of these patients indeed had varying degrees of localizing or lateralizing neurologic deficits but their major clinical syndrome was that of increased intracranial pressure.

Keep in mind from my earlier comments that the increased intracranial pressure can result from many mechanisms: the lesion may be located so far frontally or occipitally that lateralizing internal capsule dysfunction is relatively insignificant as the abscess enlarges greatly; there may be multiple lesions; there may be widespread cerebritis; there may be a component of associated hydrocephalus; and thrombophlebitis of dural venous sinuses and cortical veins may be present.

In this group, an early correct diagnosis was made clinically in five of the eight patients because of associated known facts (two adults with chronically draining mastoiditis, one teenager with rheumatic mitral stenosis and infective endocarditis, one adult with frontal sinusitis and focal fluctuance and one adult who had received a gunshot wound in that area of the brain six years earlier). The other three patients were first considered to have glioma, mental deterioration of unknown cause, and meningitis. A lumbar puncture was done on five patients: one patient had an uncal herniation syndrome within two hours of the LP; and one patient's level of consciousness declined considerably over 24 hours following an LP.

There were two deaths in this group. One patient died from overwhelming mass effects. The patient with an uncal herniation following LP was the other patient in this group to die. He had at first improved, the lesion had been localized angiographically, but two attempts at burr hole aspiration had yielded only a small amount of purulent material (about 1 ml) plus clear ventricular fluid. Multiple complications then occurred (stress ulcers, metastatic renal and abdominal abscesses and intraperitoneal bleeding) and the patient died. At autopsy, an untreated 4 by 5 cm occipital lobe abscess was found with nearby needle tracks enter-

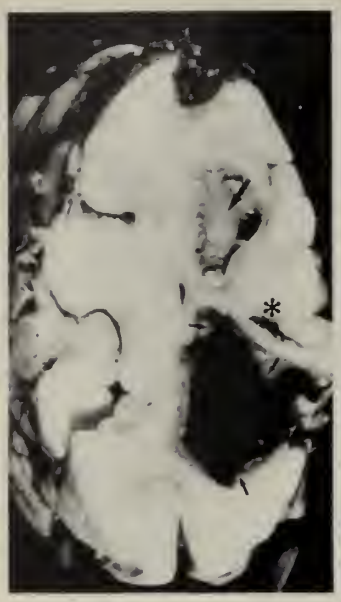

Figure 4.—Brain specimen obtained at autopsy. View of left occipital pole. The large arrow points to the abscess. Small arrows indicate inflammatory ependymal changes within the ventricle. The asterisk (*) is just above one of the cannula tracts. Cannula apparently entered the posterior horn of lateral ventricle but not the abscess.

ing the lateral ventricle (Figure 4). The abscess itself was in communication with the ventricular system and there was suppurative ependymitis. An example of a Type II lesion is illustrated in the following case.

REPORT OF A CASE

A 34-year-old man was admitted to hospital with a history of having "sinusitis" three months earlier, followed by progressive headache and more recently, confusion for two weeks before admission. On examination, a low grade fever (38°C, 100.4°F) and focal fluctuance and tenderness over the right forehead were noted. Only two abnormalities were found on neurologic examination: the patient was confused and there were two diopter papilledema. Plain x-ray studies showed frontal sinusitis and osteomyelitis. Cerebral angiography showed a right frontal avascular mass lesion. At surgical operation, a temporal burr hole was placed, the abscess aspirated and the frontal osteomyelitis was debrided. A catheter was left in the abscess cavity and intermittent irrigations and aspirations were done for six days. Penicillin G, 20 million units a day, was administered intravenously and continued for four weeks. The patient made a complete neurological recovery.

Type III abscess presentation (diffuse destruction). Three patients presented with the symptoms and signs of a diffuse, rapidly progressive, destructive brain process. The clinical progression evolved over days. The "destructive" component refers to the fact that these patients deteriorated neurologically out of proportion to their estimated intracranial pressure: two patients had no papilledema and one had only mild papilledema. They deteriorated in the absence of a brain herniation syndrome. These patients did not have any known reason for a vascular cause of their syndrome but the temporal profile of their deterioration was similar to that of a patient sustaining showers of multifocal cerebral emboli.

The three patients in this group all died and the correct diagnosis was established in each instance. One patient had poorly controlled systemic lupus erythematosus for many years and was chronically maintained on immunosuppressive levels of corticosteroids. The other two patients were in excellent health when overwhelming systemic infection developed. The duration of the illness from the first appearance of neurologic abnormalities to death was eight, ten and 24 days. Each patient had one lumbar puncture performed. There was no obvious deleterious effect of the LP but the patients had advanced neurologic deficits at the time of the study. An example of a Type III lesion is provided in the following case.

REPORT OF A CASE

A 54-year-old man was healthy and working as a landscape gardener when he developed multiple, painful pustules on his finger tips six weeks before admission. Similar painful lesions developed on his toes and then his calf ten days before admission. Profound anorexia developed. On admission, he appeared cachectic, febrile (38.4°C, 101.2°F) with multiple fluctuant lesions, both subcutaneous and intramuscular over his body. Mental activity appeared to have slowed and a mild left hemiparesis was noted. Extensive incisions and drainage were done on the peripheral abscesses; the material was foul-smelling and eventually Actinomyces was cultured. Despite vigorous local wound care and massive antibiotic therapy including penicillin and chloramphenicol, he steadily deteriorated neurologically. Over the next seven days, he became comatose with only lower brain stem function preserved. Results of LP showed nine leukocytes per cu mm (three neutrophils and six lymphocytes) and negative culture. Brain scan was diffusely abnormal over the right hemisphere and bilateral carotid angiography showed some vascular spasm with no localized mass lesion. The patient died ten days after the onset of his hemiparesis. At autopsy, numerous cerebral and meningeal abscesses were seen of

varying size and age, with widespread edema surrounding the lesions. There was no evidence of infective endocarditis.

Type IV abscess presentation (focal neurologic deficit). Three patients presented with the symptoms and signs of focal neurologic deficit. The temporal profile was that of a very slowly expanding lesion. In each case, the major clinical diagnosis was that of a meningioma and in two patients the differential diagnosis included a slowly growing benign glioma. The diagnosis of meningioma (versus glioma) was believed to be correct even after cerebral angiographic studies. In one patient there was transiently exacerbated left hemiparesis following a pneumoencephalogram. In the other two patients there were no detectable consequences of lumbar puncture. In another patient, a diagnosis of abscess was not considered despite the history of an earlier compound, comminuted skull fracture overlying the angiographically demonstrated mass. However, the fracture had occurred 14 years earlier. At operation, a bone fragment was found within one of four contiguous but loculated abscess cavities. An example of a Type IV lesion is provided in the following case.

REPORT OF A CASE

A 61-year-old man complained of visual disturbances for about two months. The only abnormality on examination was a complete left homonymous hemianopsia. Approximately two weeks before the onset of visual symptoms, the patient had an episode of diverticulitis with fever. Although he first became afebrile after treatment with antibiotics, there were several periods of recurrent febrile episodes requiring additional courses of antibiotic therapy. Angiography and pneumoencephalography showed a right occipital and posterior temporal mass. Needle biopsy through a burr hole led to the correct diagnosis of brain abscess and the initial therapy was direct aspiration and intravenously administered penicillin. Two weeks later, the abscess was totally excised. The patient then recovered gradually but had a sustained homonymous hemianopsia.

Recapitulation and Formulation of Diagnostic Evaluation

I have emphasized that the patient with a brain abscess does not present with a problem of the diagnostic work-up of a brain abscess. These patients present with clinical problems predominantly caused by major alterations of intracranial mass dynamics. Perhaps in one-half of all such cases there is antecedent history or physical signs that lead to a realistic consideration of the possibility of a brain abscess. Usually "brain abscess" at best is included in a working differential diagnosis after a careful history and physical examination.

Since brain abscesses most often cause intracranial hypertension and brain shifts (incipient herniations), it is axiomatic that the entire patient work-up and therapy be planned with this in mind. Several key points should be emphasized.

A lumbar puncture is extremely hazardous and does not yield critical information. A brain abscess uncommonly presents as "meningitis," so theoretically LP's should be quite uncommon in these patients. However, clinical surveys repeatedly show frequent LP catastrophes in brain abscess patients.[1,3,4] Even when the LP is done with a relatively small-bore needle and only 1 to 3 ml of CSF is intentionally withdrawn, the recently needled dura-arachnoid opening may persist because of the increased intracranial pressure and a slow unseen CSF leak may continue into deep paraspinous musculature. Thus, the major herniation following LP may occur minutes to hours after the procedure.

In the infrequent patient in whom meningitis was suspected but only normal CSF was found (or CSF changes were inadequate to correlate with symptoms and signs), the physician should be especially alert for any subsequent neurologic changes. (The rare abscess leaking into ventricle or subarachnoid space will obviously still remain a consultant's challenge.) Therefore, even with suspected "intracranial infection" there should not be a conditioned reflex to perform an LP. An LP is urgently needed in a patient with meningitis but is hazardous in a patient with brain abscess (and in subdural empyema).

Those maneuvers that cause hypercarbia or potential hypoxia (sedating patients for headache or too much premedication for diagnostic studies) are hazardous to the brain because of deleterious effects on cerebral blood flow. Any Valsalva maneuver is hazardous because of decreased venous drainage and subsequently increased intracranial pressure. Valsalva can occur with a sedated (or neurologically obtunded) patient developing obstructed breathing or with inattention to straining caused by constipated stool. Excessive intravenous hydration can abruptly worsen the associated cerebral edema.

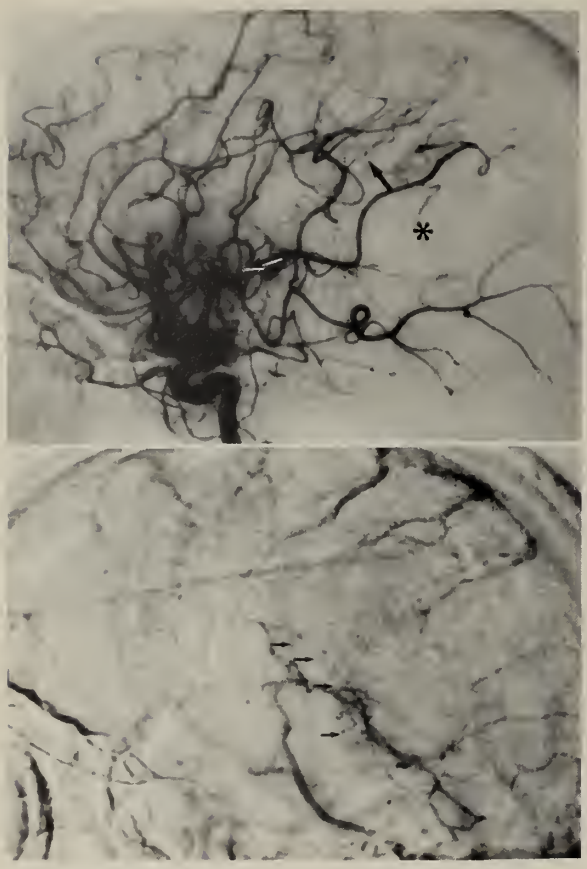

Figure 5.—Upper, lateral view, arterial phase of a selective internal carotid angiogram. Asterisk (*) is in the center of an avascular mass. The upper large arrow indicates displacement forward of parietal lobe vessels. Lower arrow indicates temporal lobe effect in that the middle cerebral artery is displaced forward. **Lower,** lateral view, venous phase of same study depicted in upper frame. Arrows point to abnormal subependymal and deep white matter veins. Neuroradiological impression was a large occipital lobe mass, "probably a primary glioma."

In summary, the diagnostic evaluation must begin with disease recognition and must continue with the patient's safety assured by an understanding of those maneuvers constituting a grave danger to the intracranial hypertension. If the patient's clinical course is not rapidly worsening, brain scan and electroencephalogram are two safe studies that may often provide useful information. Cerebral angiography must be done at some point for a more precise understanding of the lesion (Figure 5).

If the patient's clinical condition is precarious, angiography should be the first diagnostic procedure to be done when the diagnosis of brain abscess is considered. Depending on the clinical symptoms and signs, the angiographic study may have to be performed through both internal carotid arteries as well as through the vertebral system. Therefore, at all three hospitals reviewed for this symposium, the route of choice for cerebral angiography has been transfemoral for the past ten years. Once the angiographic catheter has been passed into the thoracic aorta, it can be successfully guided into the orifices of any major cerebral artery. (The specific and nonspecific findings on EEG, brain scan and cerebral angiography will not be discussed. This subject is not as important as improving disease recognition and suspicion.)

Microbial Flora

THOMAS T. YOSHIKAWA, MD: The microbial flora of brain abscess has been traditionally reported as involving a variety of organisms with a predominance of aerobic streptococci and coagulase-positive staphylococci. However, with the recent development of more sophisticated anaerobic bacteriological techniques, the role of anaerobes in brain abscess has become increasingly important. Before discussing in detail the specific microbial flora isolated from brain abscesses, a review should be made of the various factors which may be relevant in determining the types of microorganisms often recovered from this infection.

Four determinants appear to be most important in the ultimate microbial flora of brain abscess:

1. The primary source of infection or predisposing factors to brain abscess.
2. The age of the patient.
3. The patient's basic underlying disease or immune status.
4. Previous use of antibiotics.

Primary source of infection or predisposing factors

Ear, mastoid and sinus infections. Chronic otitis media or mastoiditis along with paranasal sinusitis are among the most common sources of infections preceding the development of brain abscess. The pathogenesis of brain abscess from these infected sites is usually by direct extension from the primary infected site to the brain or by retrograde thrombophlebitis via various venous channels connecting either the ear structures or sinuses to cerebral cortex.[5] Although data obtained by careful anaerobic isolation techniques on the microbial flora of chronic ear infection are not available, by inference, it would be anticipated that anaerobic bacteria may play a more significant role in chronic ear infections. One-half of Heineman and

Braude's[6] cases of anaerobic brain abscess were associated with ear infections and in each instance anaerobes were isolated from the abscess fluid. Data from patients with chronic sinusitis has been more readily available.

A recent study of 83 patients with paranasal sinus infections[7] showed anaerobes to be present in 52 percent of the cases while aerobes were present in 43 percent with mixed infections commonly found. Of the 28 specimens (30 percent of cases) with heavy growth of organisms, 23 were due to anaerobes alone and only three due to aerobes alone while in two instances, mixed anaerobic and aerobic flora were found. The predominant anaerobes were streptococci (anaerobic or microaerophilic). However, Bacteroides species were recovered in nine instances as a pure heavy growth, four being Bacteroides fragilis. Although not recovered in heavy growth, Staphylococcus aureus and Streptococcus viridans were the most common aerobes isolated.

Metastatic. Hematogenous or metastatic spread of infection from distant foci has been, in many reported series, the most common cause of brain abscess. Lower respiratory tract infection, especially chronic empyema, lung abscess and bronchiectasis, is commonly found. Organisms frequently associated with these infections have been anaerobic and microaerophilic streptococci, Fusobacterium, staphylococci, Klebsiella, pneumococci and occasionally Actinomyces and Nocardia. Other peripheral infections associated with brain abscess have been cellulitis, postoperative intra-abdominal and wound infections, osteomyelitis and pelvic inflammatory disease. Additionally, it should be remembered that infective endocarditis is not an uncommon cause of brain abscess. In fact, it is only after the diagnosis of a brain abscess is made that some cases of endocarditis are suspected. With infective endocarditis, the cerebral abscesses tend to be multiple, are usually relatively small in size and often associated with a mild to moderate degree of leptomeningitis. The presence of a coagulase-positive staphylococcal brain abscess or meningitis in the absence of cranial injury or infected peripheral foci should make one strongly suspect infective endocarditis, especially if the patient is young and has a history of drug abuse.

Cranial trauma or surgery. Direct head trauma or penetrating wounds to the skull can lead to brain abscess either by direct implantation of micro-organisms into cerebral tissue or by extension of secondarily infected scalp, bone flap or cranial osteomyelitis. Similarly, surgical craniotomy can lead to brain abscess. The most common bacteria associated with these injuries is Staphylococcus aureus. Occasionally aerobic Gram-negative bacilli, especially Pseudomonas aeruginosa, can be found in these infections.

Congenital heart disease with right-to-left shunt. Cyanotic heart disease is a frequent cause of brain abscess. The postulate is that the usual "normal" bacteremia one encounters daily is generally, in part, filtered out of the circulation by the lungs. However, with a right-to-left shunt, bacteremia bypasses the lung and can reach peripheral sites, including the brain. The microbial flora will depend on the type of peripheral infection and bacteremia involved. The brain may be prone to infection in these patients because of polycythemia and resultant intravascular thrombosis and infarction. The thrombosis may be from peripheral vein clots reaching the cerebral circulation as a paradoxical embolus, or from *in situ* thrombosis or embolism from cardiac chambers.[8]

Age of patient. The age of the patient is a determining factor largely in the pediatric group. Neonatal infections are generally due to Gram-negative bacilli and Staphylococcus aureus. Children up to the age of ten years will often become infected with Hemophilus influenza, commonly in the upper respiratory tract, ears and sinuses. At the other end of the age spectrum, older patients may be more prone to Gram-negative and staphylococcal infections, perhaps due to frequent hospital admissions with greater risk to hospital-acquired infections or associated underlying disease.

Underlying disease or immune status. Certain disease states are commonly associated with particular types of infecting organisms. A few examples would be sickle cell disease with Salmonella or pneumococci; alcoholic liver disease with pneumococci, Klebsiella or E. coli; prosthesis (heart valves, ventriculo-jugular shunts and the like) with coagulase-negative or -positive staphylococci; heroin addiction with Staphylococcus aureus, Candida or Gram-negative bacilli, especially Pseudomonas; and burn patients with infections due to Pseudomonas aeruginosa. Additionally, patients with lymphoma, leukemia or cancer or abnormal immune defense mechanisms secondary to drug therapy (steroids, anti-neoplastic agents) can develop brain abscess due to unusual micro-organisms.

In a recent report by Chernik et al[9] describing central nervous system infections in cancer patients, 39 patients had brain abscess; almost one-half of these were due to Gram-negative bacilli and one-third were caused by fungi (Aspergillus, Mucor, Candida and Nocardia). Two patients had brain abscess due to Toxoplasma gondii.

Previous use of antibiotics. Not uncommonly, patients are often given antibiotics for various types of infections before the clinical onset of brain abscess. Under these conditions, it is predictably more difficult to anticipate the type of microbial flora that might be found at the time brain abscess is diagnosed. The usual aerobic and anaerobic flora of the primary disease or predisposing factors to brain abscess may be replaced by other less commonly found microorganisms. This frequently occurs in the hospital patient receiving antibiotics where the usual mouth and respiratory tract microbial flora is replaced by Gram-negative bacilli or staphylococci.

Despite the emphasis on the four major determinants of the microbial flora of brain abscess, most centers reporting their experiences with this disease have consistently demonstrated the streptococci and staphylococci as the most common pathogens. However, the majority of these reports failed to utilize careful anaerobic isolation techniques to identify the bacteriology of brain abscess.

Heineman and Braude[6] provided a major breakthrough in this regard by carefully studying 18 cases of brain abscess not associated with cranial trauma or congenital heart disease. Using careful aerobic and anaerobic techniques, they demonstrated some interesting data. Aerobic cultures yielded organisms in only six instances with 12 patients having "sterile" brain abscess cultures. However, anaerobic cultures were sterile in only three instances. Anaerobic or microaerophilic streptococci comprised the majority of total isolates but Bacteroides were recovered in seven instances, three due to Bacteroides fragilis.

Since then, other reports have reaffirmed the role of anaerobes in brain abscess.[10,11] Thus, the so-called "sterile" cultures reported in brain abscess may indeed be in part due to the failure of recovering anaerobes. Anaerobes are fastidious microorganisms which survive only under conditions of low oxidation-reduction potential (oxygen-free environment). The collection of the brain abscess material in oxygen-free transport containers is extremely important. Failure to adhere to this practice will result in poor yield of anaerobes regardless of whatever sophisticated anaerobic culture method is used. Although there are some differences in the type of anaerobic culture techniques used by various centers, the Infectious Disease Research Laboratory at Harbor General Hospital has adopted the Virginia Polytechnic Institute method.[12] Details of this method are beyond the scope of our discussion. However, it is hoped that most hospital clinical microbiology laboratories will eventually use some acceptable form of anaerobic bacteriological technique. The clinical relevance of anaerobes in brain abscess will be discussed further under antibiotic therapy.

Antibiotic Therapy

Once the diagnosis of brain abscess has been established clinically, systemic antibiotic therapy should be administered before surgical drainage unless surgical operation is contemplated in the immediate future. Although several reports have presumed that the "sterile" cultures obtained from brain abscesses may have been due to prior antibiotic therapy, there have been no conclusive data to confirm this. Indeed, a recent careful study of six consecutive patients with brain abscesses treated with systemic antibiotics showed that organisms could be recovered from brain abscesses aspirated in all patients.[13] This occurred despite therapeutic concentrations of antibiotics in five of the six brain abscess aspirates. Again, the "sterile" cultures reported by other investigators may be related to the failure of isolating anaerobic bacteria. The importance of initiating systemic antimicrobial therapy early is two-fold. First, the associated cerebritis with brain abscess can only be effectively managed by antibiotic therapy. Second, local tissue contamination and possible bacteremia during surgical operation may be minimized with preoperative chemotherapy.

In determining the appropriate antibiotic before surgical drainage, the physician should be aware of the four determinants previously discussed and select the drug according to the microorganism most likely to be found. Generally speaking, most brain abscesses will have organisms sensitive to penicillin. In the absence of clinical clues as to the most likely infecting agent, penicillin G would be the drug of choice and should be administered intravenously in four to six divided doses totalling twenty million units a day. If staphylococcus is suspected, a penicillinase resistant penicillin, such as methicillin, should be added. If the patient has a

definite penicillin allergy chloramphenicol should be substituted for penicillin in a dose of 4 grams a day administered intravenously. The cephalosporins, especially cephalothin (Keflin®) and clindamycin (Cleocin®) do not cross the blood-brain barrier very well and, therefore, are not recommended.

The single most important diagnostic tool available in making a decision concerning antibiotic therapy is the Gram stain. At the time of surgical drainage of the brain abscess, the abscess fluid must be Gram stained. The presence of thin non-pleomorphic Gram-negative bacilli suggests Bacteroides, and the possibility of B. fragilis cannot be excluded. This latter organism is resistant to penicillin[14] and over one-half of the strains are not susceptible to tetracycline.[15] Chloramphenicol would be the drug of choice in the initial therapy before sensitivity data are available in this situation. Organisms which are Gram-positive branching rods might suggest Actinomyces or Nocardia, the latter often being weakly acid-fast and requiring sulfonamide therapy while the former would be best treated with penicillin. Large Gram-positive cocci most often are staphylococci and methicillin, or nafcillin would be indicated. Therefore, the Gram stain is extremely helpful in determining initial antibiotic therapy before culture results. Once the culture data are available, necessary adjustments in chemotherapy can be made. Brain abscess fluid must be cultured aerobically and anaerobically. Again, transport of the material in oxygen-free containers is extremely important. Cultures for fungi should also be obtained.

Despite the importance of antibiotic therapy, it should be emphasized that a cure for brain abscess (like any other abscess) can only be achieved by concomitant adequate surgical drainage. This therapeutic aspect will be discussed by Dr. Goodman. Additionally, it should be remembered that the primary foci of infection must also be adequately treated (such as drainage of infected sinuses, mastoidectomy, drainage of empyema and removal of infected prosthetic devices). One last comment on therapy pertains to the intracavitary local instillation of antibiotics. Mechanical irrigation undoubtedly aids in removing necrotic and infected material, but the direct bactericidal effect of local antibiotics remains to be proven.

Surgical Therapy

Dr Goodman: There are two surgical approaches available in treating brain abscess: drainage or excision. Each approach has a number of variations. In addition, there are several adjunctive measures that can be used to supplement surgical therapy. Finally, important clinical determinants of surgical therapy are the status of the patient and the manner in which the diagnosis of brain abscess was made (for example, was the diagnosis made preoperatively or was the diagnosis made unexpectedly in the operating room?).

Figure 6.—Immediate post-operative skull x-ray film showing strategic placement of a burr hole in patient depicted in Figure 5. Small arrows outline craniotomy used to approach occipital mass. Wire skin sutures are still in place. After the abscess was encountered, the bone flap was secured to the skull and a burr hole was centrally placed (large arrow) as close as possible to abscess. A catheter can be seen passing through burr hole into abscess cavity. Contrast material can be seen in cavity.

Drainage of the abscess means drainage of necrotic and purulent material externally. A burr hole is strategically placed which provides: (1) the shortest distance between dura and the depth of abscess; (2) a safe trajectory between dura and abscess that does not traverse crucial structures whether neural (for example, motor cortex), vascular, or ventricular and (3) a route not passing through infected bone, paranasal sinuses, or other skull infection. If the first burr hole does not satisfy all these requirements, a second is placed (Figure 6). Through the burr hole a catheter can be placed, providing a route for aspiration and irrigation. Or, the burr hole can be used intermittently for brief, repetitive reintroduction of an aspirating or irrigating cannula. Cannula placement can be done by experienced "dead reckoning" or with fluoroscopic aid, or with full stereotaxic support equipment. Often a catheter is used for three to five days and thereafter the abscess is aspirated as needed with a cannula. Drainage

Figure 7.—Upper, abscess cavity outlined by a radiopaque marker approximately 12 days following surgery. Notice the more spherical distribution of the marker compared to Figure 6, and the two irregular posteriorly pointing extensions of the cavity. **Lower,** same patient six months following surgery. The general shape of the abscess cavity has remained unchanged but there has been substantial reduction in the volume of the cavity.

requires that there be a precise understanding of the abscess size and shape so that the most basic judgment can be made daily (such as is the abscess getting bigger or smaller?). Air can be injected into the cavity so that it can be visualized on plain x-ray films. Microbarium sulfate can be injected, and *if* it becomes evenly distributed in the cavity, and *if* it is taken up by the glial lining cells, a convenient radiopaque marker may be visualized (Figure 7). Finally, angiographic, pneumoencephalographic or ventriculographic techniques can be used to delineate the abscess size.

Drainage techniques are simple. The burr hole can be placed with just local anesthesia, and repetitive manipulation of the abscess cavity thereafter is a ward procedure. The major disadvantage is that daughter abscesses may be undetected and untreated. The condition of a patient could precipitously worsen from a daughter abscess spatially related to the main abscess but unrelieved by the percutaneous techniques directed to the main abscess. Intracavitary air or microbarium sulfate may simply lull the physician into assuming gains are being made while daughter abscesses are worsening. Considerable skill and clinical acumen are needed in correlating the clinical course with the neuroanatomic geometric problem.

Excision, or "radical extirpation" refers to complete surgical removal of the abscess. To the extent that there is an organized capsule there will be a readily identifiable brain-abscess interface permitting abscess removal with a minimum of damage to surrounding brain. Radical extirpation removes all daughter abscesses and, therefore, provides the lowest abscess recurrence rate. However, not all lesions can be treated this way. The abscess might be too hazardously deep (thalamic or brain stem) or the abscess might not be sufficiently localized and walled off. (A late complication of brain abscess is seizures. This complication is unaltered by radical extirpation.) Radical extirpation is often done as a secondary procedure after initial abscess drainage, with the initial procedure yielding benefits of organism identification, optimal chemotherapy, decreased mass size and neurologic improvement.

Adjunctive measures are used, as needed, to supplement surgical therapy when the intracranial mass effects and the degree of intracranial hypertension is life-threatening. A detailed discussion of these techniques is beyond the scope of this conference. The techniques that can be marshalled include controlled hyperventilation, acute or semichronic dehydration, steroid administration, hypothermia, "external" (skull) or "internal" (brain) decompression and ventricular drainage.

The clinical setting in which the diagnosis is made is probably the most important determinant of the surgical therapy employed. Patients presenting with Types I, II and III syndromes have rapidly progressive lesions, have ominous, decompensated intracranial mass dynamics and probably have less mature abscess capsules. These patients are most appropriately treated by abscess drainage techniques. Patients presenting with a Type IV syndrome could have primary radical extirpation of a favorable superficial lesion, but since the diagnosis was probably unanticipated, a period of abscess drainage would allow optimal chemotherapy to be started before abscess excision. We prefer, whenever possible and clinically reasonable, to first drain the abscess and then employ

a secondary procedure and radically extirpate the remaining abscess several days or weeks later.

Regardless of the modes of therapy or types of antibiotic used, the prognosis of patients with brain abscess is directly related to the neurological status of the patient when therapy is begun.[4] The major challenge in treating patients with brain abscess is physician education so that the clinical suspicion occurs earlier, patient evaluation is expedited quickly and safely, and antibiotic and surgical therapy are begun relatively early in the unfolding sequence of pathophysiological events.

Trade and Generic Names of Drugs

Cleocin® ..... clindamycin
Chloromycetin® ..... chloramphenicol
Keflin® ..... cephalothin
Garamycin® ..... gentamicin
Staphicillin® ..... methicillin
Lincocin® ..... lincomycin
Unipen® ..... nafcillin
Dynapen®, Pathocil®, Veracillin® .... dicloxacillin
Fungizone® ..... amphotericin B
Polycillin®, Omnipen®, Totacillin®, Amcill®, Penbritin®, Principen® .... ampicillin
Penicillin G ..... penicillin G

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Informed Consent in California

If you're going to give medical therapy that amounts to anything, you'd better briefly but clearly mention the problems to the patient. For example, let's suppose that you have a glaucoma patient come in for the first time. You would, I think, say to him that the medical therapy of glaucoma does involve certain risks and certain problems . . . and obviously mention the effect of the drug on his vision and the possibility of allergies. Then note in your chart: "The medical therapy of glaucoma, including risks and alternatives, was discussed." And date it and sign it. It is important to know that juries believe almost everything that is written in a chart and almost nothing that is not written in a chart. So keep that clearly in mind . . .

—Jerome W. Bettman, MD, *Stanford, CA*
Extracted from *Audio-Digest Ophthalmology*, Vol. 12, No. 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Important Advances in Clinical Medicine

Epitomes of Progress—General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in General Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in General Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Acute Arterial Thrombosis

ACUTE ARTERIAL THROMBOSIS is relatively uncommon in the spectrum of arterial occlusive disorders. However, because of its catastrophic nature and special therapeutic requirements it must be quickly differentiated from the more common embolus, which it can closely mimic. The rapidity of the process precludes the collateral compensation seen in chronic occlusions and tissue loss is eminent.

There is an extensive list of disease states associated with acute arterial thrombosis but the pathogenesis, originally described by Virchow, is relatively constant and involves no more than three factors. The most easily appreciated is a change in the arterial wall. This is usually the result of one of the degenerative diseases, most commonly atherosclerosis, but may also be secondary to inflammation (arteritis) or trauma of even a minor nature. In some young patients hypoplastic vessels have been found. The second factor sometimes seen is an alteration in the blood composition producing a hypercoagulable state. This might occur with the myeloproliferative disorders or after trauma. Finally, a sudden decrease in the rate of blood flow is commonly found just before thrombosis. This may be the result of a decrease in cardiac output, hypovolemia or a generalized loss of vascular tone.

The diagnosis can be established clinically, though arteriography is helpful in the general vascular evaluation. There are always rest pain, signs of ischemia and a lack of pulses in the involved area. There will usually be no apparant (cardiac) source for an embolus. This is the clinical clue that these signs and symptoms are manifestations of acute thrombosis and not embolus. The lower

half of the body is most commonly affected because of the common association of atherosclerosis and a propensity for decreased flow states. In decreasing order the femoral, popliteal, iliac arteries and aorta will be involved. Acute arterial thrombosis in the arms or neck (excluding a cerebrovascular accident) is unusual and often associated with trauma.

The exclusion of an embolus is therapeutically important because standard methods of embolectomy, though relatively safe and uncomplicated, are usually futile when acute thrombosis is present. An unsuccessful embolectomy in such a patient should alert the surgeon to possible acute thrombosis. When further attempted in these patients it may unnecessarily jeopardize limb and life. The best results have been achieved with emergent arterial reconstruction, preferably with a bypass procedure or, if the thrombosis is localized, endarterectomy. With this aggressive approach, limb salvage can be achieved in over 90 percent of cases and the rate of survival increased over that achieved with lesser procedures.

LAWRENCE A. DANTO, MD

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Aortoiliac Steal Syndrome

KOUNTZ, LAUB AND CONNOLLY described a new syndrome in 1966 in which blood is shunted away from the mesenteric arterial bed into disobliterated or bypassed peripheral arteries. This stealing of blood from the mesenteric circulation can result in gangrene of the bowel after a reconstructive operation on the aortoiliofemoral vessels. This syndrome was called the aortoiliac steal syndrome.

Animal experiments by the original authors showed that lumbar sympathectomy or iliac bypass grafting steals blood from the superior mesenteric artery in an inverse relationship to the amount of new blood diverted peripherally by the procedure.

Such stealing is normally tolerated by the mesenteric circulation unless it is severely compromised. Preoperative compromise of the mesenteric circulation is identified by the presence of an enlarged central anastomotic artery on aortography. An enlarged central anastomotic artery always means pronounced stenosis or obstruction of two of the three mesenteric takeoff vessels.

A number of clinical reports of gangrene of the bowel secondary to the aortoiliac steal syndrome have appeared since 1966 and underscore the need for understanding this syndrome by those performing peripheral vascular surgical procedures.

JOHN E. CONNOLLY, MD

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Resection of Aortic Arch Aneurysms

UNTIL RECENTLY, resection of aortic arch aneurysms with prosthetic graft replacement was a hazardous undertaking, owing largely to the complicated perfusion apparatus that has been used for circulatory support during operation. To provide complete perfusion of vital organs, inflow catheters must be placed in the innominate artery, the left carotid artery, the left brachial artery and a femoral artery. The problems of adjusting pressures and flow rates in these multiple infusion lines have generally resulted in uneven perfusion of various portions of the circulation with resulting ischemic damage.

Recently the success of the technique of total body hypothermia and circulatory arrest in dealing with complex congenital heart lesions in infants has suggested that with modification the technique might be applicable to the adult. In adult dogs if the brain temperature is less than 20°C, periods of circulatory arrest up to one hour are well tolerated. Based on these findings a technique has been developed which allows replacement of the aortic arch with the same operative risk as replacement of any other portion of the intrathoracic aorta.

Our present technique for aortic arch replacement is as follows. Following induction of anesthesia, surface cooling lowers the patient's temperature to 30°C. A median sternotomy with an

extension to the left supraclavicular area is made, and the aortic arch and its three major branches are dissected. Cardiopulmonary bypass is instituted with an inflow cannula in the femoral artery, and vena caval catheters inserted through the right atrium. A heat exchanger in the bypass circuit lowers the patient's temperature to 20°C. The circulation is stopped, and the patient's temperature drifts down to 12 to 15°C. The aortic arch vessels and the descending thoracic aorta are clamped, and the aortic arch is opened. An ellipse of aorta containing the orifices of three arch vessels is tailored and prepared for anastomosis. A dacron graft is anastomosed end-to-end to the descending thoracic aorta. A slit is cut in the superior aspect of the graft, and the ellipse of the aorta containing the arch vessels is sewn into the graft. A cross-clamp is placed around the graft proximal to the arch vessels, the other vascular clamps are removed and cardiopulmonary bypass is reinstituted. Using surface warming and a heat exchanger, the patient's temperature is brought to normal during anastomosis of the graft to the ascending aorta or, if the ascending aorta requires replacement, to the aortic annulus.

With an average-sized adult the period of core cooling is approximately 30 minutes, the period of circulatory arrest is 30 to 40 minutes and the period required for warming is one to one and a half hours. Patients awaken promptly, and in most cases ventilatory support is discontinued and ambulation is begun on the first postoperative day.

RANDALL B. GRIEPP, MD

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Intestinal Bypass in the Treatment of Obesity

SHORTENING THE FUNCTIONAL intestinal tract by jejunocolostomy to cure intractable obesity fell into disrepute when the operation resulted in serious, sometimes fatal deficiency syndromes. During the past ten years the end-to-side jejunoileostomy introduced by Payne in Los Angeles has achieved increasingly wide acceptance as a safe and effective surgical cure of morbid obesity.

More recently, Scott's end-to-end jejunoileostomy and Printen's gastric bypass have been introduced in an attempt to improve the results, but it is too soon to evaluate comparable long-term follow-up.

There are now hundreds of patients in many cities who have been given a new lease on life by the only treatment for massive obesity so far devised with a minimal recurrence rate.

MARVIN L. GERBER, MD

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Pancreatic Trauma: Management and Presentation of a New Technique

INJURIES TO THE RETROPERITONEAL ORGANS, including the pancreas, are increasing in association with the high incidence of abdominal trauma caused by highway accidents. Because of its relatively protected retroperitoneal position, the injuries to the pancreas account for only 1 to 2 percent of all traumatic abdominal injuries. The types of treatment used for pancreatic injury are as varied as the location and extent of damage to this organ.

Damage to the pancreatic head requires special consideration. There are two alternatives when treating injuries in this area. One is external drainage with or without suture repair and the other is pancreaticoduodenectomy. Contusions of the pancreatic head, small parenchymal lacerations and occasionally low velocity, through-and-through gunshot wounds may be managed by external drainage alone. Pancreaticoduodenectomy is done when there is extensive devitalization of the pancreatic head, complete proximal ductal disruption, uncontrollable bleeding from the injured area or extensive devitalization of the duodenum. The rate of mortality following pancreaticoduodenectomy and reestablishment of gastrointestinal continuity is high because of inability of the patients to sustain the traumatic injury and the superimposed surgical trauma. In selected cases it may be preferable to resect the stomach, duodenum and pancreas, and exteriorize the en-

tire gastrointestinal tract to be later reconstructed in stages. This procedure was designed to decrease the mortality rate associated with pancreaticoduodenectomy when it is required in severely traumatized patients.

EARL F. WOLFMAN, JR., MD

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Intraoperative Autologous Autotransfusion

REINFUSION OF AUTOLOGOUS BLOOD to provide a readily available, hepatitis-free intraoperative blood source has been proposed as a solution to critical shortages of banked blood. Three techniques have been used successfully: (1) preoperative self-donation with storage by red cell freezing or citrate phosphate dextrose anticoagulation, (2) early intraoperative phlebotomy and crytalloid volume replacement with readministration of the stored fresh blood at the end of the procedure and (3) intraoperative autotransfusion. All of these techniques have been used during elective operations, but only the third lends itself readily to an emergency situation.

The concept of transfusing blood salvaged during surgical procedures by means of an extracorporeal system was first recorded in 1818. Within the past ten years laboratory and clinical reports have been published and sterile, disposable autotransfusion systems have become readily available commercially. Animal studies of autotransfusion have used flows up to 1,000 ml per minute to volumes twice the total blood volume of the subject. Clinical reports include autotransfusion volumes up to 18 liters.

In an emergency situation the available equipment can be prepared in ten minutes to prevent uncrossmatched blood from being used in treating massive intracavitary hemorrhage. Total heparinization, 1.5 to 3 mg per kilogram of body weight, to prevent *in vitro* coagulation is recommended by several authors, even in massive trauma. Others have used incremental hemodilution and heparinization of only the aspirated blood or no anticoagulation at all. The system is primed with a solution similar to that used in cardiopulmonary bypass. Acidosis due to ischemia of major vessel clamping or low volume hypotension is combatted with bicarbonate. To assist in adequate urine formation in the face of reduced renal perfusion or traumatic hemolysis, hyperosmolar diuresis is achieved with mannitol.

As with many new techniques purported to solve existing problems, new hazards are introduced. Most of the problems associated with autotransfusion, such as air embolus, are within the control of a trained operator. Those who would use this system but are unfamiliar with extracorporeal circulation should familiarize themselves with the available literature which elucidates the fundamental problems of autotransfusion systems and the manner in which they can be safely applied.

DELFIN J. BELTRAN, MD

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Tissue Transplantation with Microvascular Surgery

MICROVASCULAR ANASTOMOSIS of blood vessels 0.6 mm to 2.0 mm in diameter is a new surgical technique with a success rate of over 90 percent in experimental models. This technique can now be applied to clinical reconstructive surgery. The two applications are digit reimplantation and skin island pedicle transplantation. Digits can be reimplanted or transplanted following traumatic amputations, for congenital absence of digits or when digits have been amputated for neoplasm or metabolic diseases. The success rates for digit reimplantation as reported by surgeons in China, Japan, Australia and the United States vary from 50 to 84 percent. There are specific indications and contraindications to digit reimplantation.

Large islands of skin and subcutaneous tissue which have been isolated on an arterial-venous pedicle can be transplanted by microvascular anastomosis. The anatomic sites for donor skin pedicles (autologous transplantation) have been delineated and successful transplant of skin flaps has been achieved. At present, there are limited applications for this technique and it has not supplanted existing methods of flap transfer. Only

when control of the skin rejection process has been achieved will there be wide application of skin pedicle transplantation.

ERNEST N. KAPLAN, MD

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Abdominal Ultrasound in Assessing the Surgical Abdomen

BECAUSE IT CAN visually depict cross-sectional and saggital anatomy and can delineate abnormal structures and distinguish whether they are cystic or solid, the use of ultrasound offers unique promise in assessing the abdomen before surgical operation.

Diagnostic ultrasound uses repetitive pulses of sound with frequencies far above the range of human hearing. At these frequencies the sound waves can be concentrated into a narrow, well-directed column, capable of penetrating the soft tissues of the body. As these waves traverse the abdomen they are partially reflected at tissue interfaces because of relative differences in acoustical impedance. Returning echoes are accumulated on a storage oscilloscope, and by this means an accurate two-dimensional anatomic section is built up. By varying the receiver sensitivity, cystic structures can be distinguished from those that are solid.

The applicability of diagnostic ultrasound in assessing the surgical abdomen is extensive. What follows is a brief and by no means all-inclusive review.

In evaluating patients with abdominal trauma, ultrasound can successfully delineate hematomas, whether they are perihepatic, perisplenic, perinephric or retroperitoneal. It can also detect the presence of blood (or other fluids) within the peritoneal cavity.

When conventional radiographic methods have failed to show a cause of jaundice, ultrasonography can demonstrate the size of the gallbladder, its response to fatty meals and, inferentially, whether or not there is obstruction. The technique also permits, with reasonable accuracy, the visualization of gallstones. Obstructive causes other than stones (for example, pancreatic carcinoma) can also be detected.

Because cystic structures (for example, pancreatic pseudocysts, renal and ovarian cysts) may be causally related to abdominal pain, the ability of ultrasound to accurately diagnose and localize these cysts is of obvious clinical benefit.

The verification or exclusion of a suspected intra-abdominal abscess is a common surgical problem. Ultrasonography can help in resolving this problem by showing abscesses, especially those of the para-appendiceal, pelvic, subphrenic and intrahepatic variety. When a technically adequate ultrasonogram fails to show an intra-abdominal abscess, such a condition may be excluded with a high degree of certainty.

Last, ultrasound is highly accurate in the detection and measurement of abdominal aortic aneurysms.

Ultrasonography is a painless, non-invasive technique, without known deleterious side effects. It represents a significant addition to the armamentarium that can be brought to bear upon the diagnosis of the abdomen before surgery.

STEPHEN I. MARGLIN, MD
ROY FILLY, MD

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Treatment of the Subclavian Steal Syndrome by Carotid-Subclavian Bypass

STENOSIS OR OCCLUSION of the proximal subclavian artery often results in retrograde flow through the ipsilateral vertebral artery. While most patients with this abnormality are asymptomatic, in some the subclavian steal syndrome develops; that is, symptoms of cerebrovascular insufficiency with or without claudication in the affected arm. This syndrome has increasingly been treated by carotid-subclavian bypass grafting to avoid the risks of thoractomy, particularly in poor risk patients. However, experimental and clinical studies indicate that, in the presence of occlusive disease of the carotid vessels, carotid-subclavian bypass may produce carotid steal with failure of the patient

to improve. Therefore, if this operation is employed in patients with occlusive disease of the ipsilateral carotid artery, it is essential that carotid endarterectomy be done in conjunction with carotid-subclavian bypass grafting.

EDWARD A. STEMMER, MD

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The Emergency Room Approach to Urethral Trauma

THE ASSOCIATION of traumatic fractures of the pelvis and lower urinary tract injuries has been well documented by numerous observers. The incidence varies from as low as 6 percent (Wakely) to as high as 25 percent (Vermooten). In evaluating the site of injury to the lower urinary tract, Clark showed that overall, 58 percent involved the urethra alone and another 9.4 percent were combined bladder and urethral injuries. These statistics should alert the emergency room physician to the high incidence of urethral injury associated with pelvic fractures.

Although death rarely results from urethral trauma, the sequelae frequently continue throughout the remainder of the patient's life. For this reason it is mandatory that the diagnosis be made in the emergency room if possible. In most instances, the emergency room physician has been conditioned to use a catheter in the severely injured patient in order to monitor his urinary output. In other cases, the physician may insert a catheter in an effort to diagnose the site of injury in the lower urinary tract. The disadvantages of this procedure are multiple. First, a partially ruptured urethra may be converted into a completely ruptured urethra. Second, a peri-vesical or peri-urethral hematoma is usually sterile but may be converted into an infected hematoma by the passage of a urethral catheter into it. Finally, the blind insertion of a catheter has the added serious risk of a false diagnosis. The catheter may be passed easily into the peri-vesical space or may curl up under the trigone giving the physician the impression that the catheter has passed through an intact urethra. This can lead to a delay of several hours before a ruptured urethra is recognized. Therefore, the insertion of a catheter has serious disadvantages which can be completely circumvented by first studying a retrograde urethrogram.

The diagnostic signs of a ruptured urethra include blood at the external meatus, inability to void, a distended bladder and superior displacement of the prostate gland on rectal examination. These signs may not all be present, however, especially if the urethra is only partially torn. Therefore, it is recommended that a retrograde urethrogram be done in all patients with a traumatically fractured pelvis before the insertion of a catheter. Only in this way can inadvertent iatrogenic injury be avoided.

ROBERT KESSLER, MD

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Clark SS, Prudencio RF: Lower urinary tract injuries associated with pelvic fractures—Diagnosis and management. Surg Clin North Am 52:183-201, Feb 1972

Initial Treatment of Potential Peripheral Visceral or Vascular Injuries from Penetrating Trauma

PENETRATING WOUNDS which may produce a visceral or vascular injury can result from such causes as stabbing, gunshot or flying debris from an explosion. The wounding force or the depth of the wound is frequently difficult to establish from the history and physical findings. Surgical explorations of such wounds have been strongly recommended to detect and prevent complications from non-apparent visceral or vascular injuries. Prompt surgical treatment is obviously indicated in visceral injuries such as cervical tracheal or esophageal disruption, when subcutaneous emphysema is present or when deviation or displacement of these structures is noted. The same is true when a significant hematoma is present with or without expansion or there is loss of the peripheral pulse. By contrast, patients who sustain similar penetrating injuries can be safely observed if there is no clinical evidence of an associated visceral or vascular injury. If observation is instituted the patient must be followed for potential complications in an identical manner to patients in whom surgical exploration was employed. No significant morbidity has been noted when appropriate observation was employed with no clinical evidence of a

significant visceral or vascular injury. Furthermore, the rate of morbidity appears to be significantly greater in patients whose wounds were explored by surgical procedures and no significant injury was found than when similar patients were simply observed.

LINDSAY C. GETZEN, MD

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Malignant Potential of Large Congenital Nevi

THERE IS CLEAR DOCUMENTATION that large congenital nevi (giant pigmented nevus, melanocytic nevus) have a very high risk of becoming melanoma. The incidence of melanoma in congenital large nevi has been reported to be between 2 and 42 percent. The average incidence reported in the literature and in the experience at Stanford Hospital suggest that the incidence projected throughout a normal lifespan is between 10 and 20 percent. Therefore, we recommend that congenital melanocytic nevi be surgically excised and reconstructed by appropriate methods. The risk of developing a melanoma is present at all ages, although 70 percent of melanomas occur before puberty. Furthermore, there appears to be a close relationship between the histologic type of the giant nevus and the risk of malignancy. Giant nevi with a histologic pattern of a junctional nevus, neural nevus or blue nevus seem to have a high risk whereas a histologic pattern of an intradermal nevus has a lower risk. Therefore, screening biopsy specimens of the nevus may be helpful in determining the need for, and timing of, surgical excision.

The reason for the high malignant potential is not known, but is probably due to one of two factors. First, the nevus is a hamartoma comprised of melanocyte-like cells derived from the neural crest. It can be postulated that whatever teratogen caused the hamartoma has altered the genetic potential within the cell or is in itself also a carcinogen and, therefore, the individual cells are more susceptible to malignant change. The alternative explanation is that a congenital nevus is a site where there are normal melanocytes in a greater density per unit area than in normal skin and the increased frequency of malignancy is because of an increased number of melanocytes.

ERNEST N. KAPLAN, MD

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Kaplan EN: The risk of malignancy in large congenital nevi. Plast Reconstr Surg 53:421, Apr 1974

Coronary Artery Disease

NUMEROUS SURGICAL TECHNIQUES have been used over the years for the treatment of coronary artery disease. These include epicardial abrasion to ligation of the coronary sinus, placement of talc within the pericardial cavity and intramyocardial implantation of the internal mammary artery. None of them have shown any great measure of success in regard to the criteria by which any operation for coronary atherosclerosis must be judged, namely relief of angina, prevention of myocardial infarction and prolongation of life.

In the early 1960's, Sones at the Cleveland Clinic developed the technique of coronary arteriography, by which the exact location of coronary artery narrowings could be ascertained. This led Favoloro, also at Cleveland, to work out a method for direct revascularization of the heart using saphenous vein grafts to bypass these arteriographically demonstrated lesions. Since its introduction in 1967, numerous modifications and refinements of the surgical technique of aortocoronary bypass grafting have been made so that at the present time late graft patency rates ranging between 80 percent and 95 percent have been reported. Further, surgical mortality rates have been reported as low as 0.8 percent in elective cases. The clinical results of aortocoronary bypass operation, in contrast to those of previous operations for coronary atherosclerosis, have been quite good, especially in the relief of angina. In one series of patients, there was complete relief of pain in 80 percent and improvement in an additional 8 percent. Other series of patients have been reported with quite similar results. Data supporting the contention that aortocoronary bypass grafting improves longevity are not complete but suggest that the operation is effective in that re-

gard. Sones has shown in a study of 1,000 patients, some of whom were treated by surgical operation and some of whom were not, that the survival rate was in fact significantly improved by surgical operation. In particular the annual mortality rate in the medically-managed patient series averaged 9.3 percent per year over a four-year period while the annual attrition rate, including hospital mortality, in a matched group treated with surgical operation averaged 4.8 percent per year in a comparable period. Few data have yet been reported concerning the relative incidence of myocardial infarction with the two methods of treatment.

At present indications for coronary bypass operations vary widely among cardiologists and surgeons. This uncertainty stems at least in part from the lack of data comparing the outcome of surgical with medical management, particularly in regard to the relative myocardial infarction rates and the relative longevity in the two groups. However, in spite of these gaps in knowledge it has become quite evident that surgical management can relieve pain in the great majority of patients. Therefore it follows that patients with angina pectoris severe enough to interfere significantly with daily activity in spite of appropriate medication should clearly be considered for coronary arteriography and subsequent bypass operations if narrowings can be shown with radiography. Guidelines for determining the risk of such an operation, based on certain preoperative assessments, have been published. Full clarification of the surgical indications must await the conclusion of clinical trials in progress at several centers.

PHILIP OYER, MD

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EDITORIAL

Levodopa After Five Years

NEUROLOGISTS REMAIN ENTHUSIASTIC USERS of levodopa for the treatment of Parkinson's disease, and most begin therapy with this drug rather than with the more traditional anticholinergics. But, as pointed out by Drs. Markham, Treciokas and Diamond elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE, it is also apparent that many patients begin to slip backward after a period of a year or two of sustained improvement. Levodopa does not, therefore, cure Parkinson's disease, though many patients after five years are still less symptomatic than they were before treatment.

Why does it work at all? Dopaminergic neurons probably have inhibitory actions on other cells in the corpus striatum, many of which are interneurons that use acetylcholine as neurotransmitter. It is therefore suggested that the symptoms of parkinsonism may be due to a relative overactivity of striatal cholinergic interneurons brought about by a decrease in dopaminergic nigrostriatal inhibition and conceivably also by sprouting and reinnervation by other non-dopaminergic endings. These suggestions have by no means been firmly established. The effect of levodopa, then, is thought to be due to an increase in the ability of dopaminergic neurons that have their cell bodies in the substantia nigra to synthesize their neurotransmitter, implying that a boost in the amount of available precursor can increase neurotransmitter synthesis in diseased and possibly unaffected neurons. I do not know of any other disorder in which a deficiency in a metabolic end product can be overcome by administering a precursor and I suspect that many physicians were surprised when it turned out that levodopa did indeed work.

The dopamine level in substantia nigra can be viewed as a biochemical marker for a certain neuronal population. Reduction of dopamine in Parkinson's disease probably reflects degeneration of these cells and may be analogous to anatomical changes that occur in other systems disorders such as amyotrophic lateral sclerosis. The reason just one category of nerve cells degenerates in such diseases is a mystery which may need a future molecular biologist to unravel. This is all the more reason to applaud the pioneers who in the case of Parkinson's disease refused to accept the notion that you have to know the cause before you can find a treatment.

Application of this approach has not yet been successful in other diseases. Other disorders, such as benign essential tremor or progressive supranuclear palsy, that may be mis-diagnosed as Parkinson's disease are not helped by levodopa. It has been suggested that Huntington's chorea might be treated with an agent designed to increase GABA concentration since GABA (gamma-aminobutyric acid, another inhibitory transmitter) and the enzyme involved in its synthesis are decreased in striatum in this disease. However, it is likely that cholinergic neurons in striatum are also affected in advanced cases[2] and in an early case of Huntington's chorea there was little change in enzymes necessary for synthesis of either GABA or acetylcholine.[3]

In addition to benefiting parkinsonian patients and adding to our knowledge of the biochemistry and anatomy of the nigrostriatal system, the use of levodopa has produced side effects only rarely encountered before and not seen when levodopa is given to normal persons. Facial grimacing and restless movements of limbs are frequent toxic effects at maximum tolerated doses. Many patients prefer to keep these movements rather than reduce the dose of the drug. The off-on (or on-off) effect is not easily correlated with time of ingestion of levodopa. The not-yet-available peripherally acting dopa-decarboxylase inhibitors do not seem to help the on-off effect, though they do reduce the nausea and vomiting that many patients have. These agents appear to be much more satisfactory for this purpose than is alpha methyl dopa. It is also of interest that other effects of levodopa on growth hormone release, and on cardiac rhythm, do not appear to represent clinically significant problems.

As is also stressed by Dr. Markham and coworkers, the use of other treatments to supplement levodopa therapy should not be overlooked. Anticholinergics may still be a very useful adjunct in some patients. Amantadine is also said to be helpful, though some neurologists seem to have better

luck with it than others (I among them). Stereotaxic thalamotomy is now only rarely being done for lateralized tremor or rigidity, and the operation does not help the more bothersome problems of bradykinesia and poor balance.

PHILLIP D. SWANSON, MD
Professor of Medicine
Head, Division of Neurology
University of Washington
School of Medicine
Seattle

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Duty to Report Child Abuse

"MALPRACTICE LIABILITY FOR FAILING TO REPORT CHILD ABUSE" is a reprinting of an article which appeared in Volume 49, No. 2, of the *California State Bar Journal* (March-April 1974). The article represents the work and research of Richard J. Kohlman, Esq., over the past one and one-half years, and it deals with the second lawsuit in California over the past two years for a failure to report. In legalese, it is an explanation of the doctrine of negligence per se and common law medical malpractice enabling an attorney to file a suit in the civil courts on behalf of an abused child. For the physician it represents a clear warning: a failure to report suspected child abuse may mean civil liability.

While both suits have been brought in California under California law, the implication is quite strong that this type of suit would be successful in any state. The obligation of physicians to report suspected cases of child abuse, as in California, is found in the law of every state, the District of Columbia, Puerto Rico and the Virgin Islands. Coupled with this obligation is the potential civil liability for all subsequent injuries to the child when there is a failure to report suspected cases of abuse.

As a physician I would like to add that the current number of children reported for significant physical abuse in the United States is 380 per million population per year. This amounts to some 70,000 children annually. The initial mortality is 5 percent; permanent brain damage due to subdural hematoma occurs in another 5 percent. There are few diseases afflicting our children with such an incredible morbidity and mortality. Physicians, their nurses and assistants have a wonderful opportunity prenatally and postnatally and in the routine care of young children to predict, prevent and treat this devastating social and medical problem afflicting so many families.

Physicians who feel that they are doing something "against the parent" by notifying suspected cases of child abuse and aiming for early intervention to safeguard the children, should instead think of doing something "for the family." Few (less than 10 percent) of battering parents are aggressive sociopaths, paranoid schizophrenics, or plain "cruel people who torture children," although there are such persons, often impossible to treat successfully. In such cases the children have to be removed to safety and sometimes parental rights must be terminated. On the other hand, the other 90 percent of families involved respond beautifully to intensive mothering care given by sympathetic lay therapists; and they can be helped by joining Parents Anonymous, or by establishing a trusting relationship to a physician, to a public health nurse, to a social worker or any other helping person. In the great majority of cases their children can be safely returned in less than eight months after intervention begins. Clearly, therefore, the outlook is excellent and the physician's duty is unmistakable.

C. HENRY KEMPE, MD
Professor of Pediatrics
University of Colorado Medical Center
Director, The National Center for the Prevention and Treatment of Child Abuse and Neglect
Denver

Brain Abscess

THE SYMPOSIUM ON BRAIN ABSCESS presented by Drs. Yoshikawa and Goodman in this issue is an excellent review. It touches on a most appropriate set of questions. One of these is the steady mortality rate of brain abscess over the last few years. The authors make clear that there are two specific reasons for continuing high mortality. First, a brain abscess is a space occupying lesion and the mortality is more closely related to that than to the infectious aspect. Second, the lack of prompt and accurate diagnosis contributes heavily to the

problem. They point out the rapidity of worsening in patients with a brain abscess. The clinical features of the disease and methods for diagnosing it are outlined.

The dangers of lumbar puncture receive both negative and positive emphasis. As meningitis is rare with brain abscess, the information obtained from lumbar puncture is of minimal value in the diagnosis. The downhill course after puncture is well documented in the authors' series. Because of these points, the authors decry the use of the lumbar puncture—a position most neurosurgeons heartily approve.

The efficiency of electroencephalogram (EEG), brain scan and angiography in confirming and localizing the abscess is mentioned. Unfortunately, EEG's and brain scan may not be available at night or over week-ends. These procedures should be available so that patients who might be harboring an abscess may have a noninvasive procedure done soon after admission to hospital. A cautious physician may be reluctant to use angiography without the additional evidence offered by these techniques. The delay may prove disastrous for the patient.

While neurosurgeons might argue about the precise technique of surgical treatment, the importance of the likelihood of multiple or daughter abscesses is discussed. Both can be missed by needle aspiration technique. A patient known to have a brain abscess must be suspected of having another abscess adjacent or remote from the proven abscess if improvement does not promptly occur after surgical therapy.

A useful and complete review of the bacteriology of brain abscess is given. Attention is drawn to the importance of anaerobic culture techniques to insure full and accurate information. Of more importance is the emphasis on smearing and staining specimens of pus obtained at operation. A great amount of information can be obtained by that old procedure. Exotic and opportunistic organisms may be shown only by smear.

A succinct review of antibiotic drugs and appropriate use is included.

Brain abscess should be a disease with a very high cure rate. It is disappointing to note that such is not the case. Information contained in the symposium should help toward that promise.

KEMP CLARK, MD
Professor and Chairman
Division of Neurosurgery
University of Texas Southwestern Medical School
Dallas

Reaching the Unreached With Health Care

SINCE IT HAS BECOME well established that medical care can improve one's chances for continuing health and longer survival, it is not only worthwhile but important to see what can be done about reaching the unreached with it. During the last decade there have been enormous efforts in both the public and private sectors to accomplish this. The approaches have been to reduce or eliminate the financial barriers, to tinker with the delivery system or consider replacing it with another, and to try to tell the public what is good and what is bad for its health, even to try frightening people. While there has been some progress, the problems of reaching the unreached with health care have by no means been solved.

It is suggested that the unreached may be considered in three categories. First there are the under-served in geographically remote areas, sometimes referred to as the rural ghettos. Then there are the under-served in the urban ghettos who may or may not be in close proximity to every kind of health care resource but still do not get the care they need. And then there is a very large and generally overlooked group, the under-served among educated, economically self-sufficient persons who are quite capable of getting health care for themselves, but who may feel they are perfectly healthy and not in need of care, or who for some other reason may not choose to avail themselves of it. It is quite clear that there is more to the problem than is likely to be solved by removing financial barriers, by restructuring the delivery system, or by imposing a period of involuntary service upon young physicians in partial repayment of the cost of their education, as is now being proposed in some government circles.

Perhaps the time has come to consider some other factors which so far may not have been given their due, and yet affect each of the three categories of under-served to a greater or less extent. One of these is cultural attitudes toward health care. These vary among individuals and within each category of under-served. It is fallacious to

assume that, in a polyglot nation such as this, any master plan to reach everyone will solve the problems unless there is a parallel effort to identify and overcome cultural biases at whatever level of society.

Another factor to be considered is distance. In rural areas this may be large, and in urban areas it is always small at least by rural standards. For the educated and affluent it may be only a few steps or a phone call. Whatever the distance, it must be taken into account and somehow overcome whether by bringing the person to the health care or the health care to the person. The transfer of persons and information from one place to another is essential and both providers and consumers must be sufficiently motivated.

A third factor of great importance is the phenomenon of the clustering of physicians and health care resources. This is natural and even necessary for scientific, economic and cultural reasons but tends to be disregarded by health care planners. This clustering is actually essential if health care of high quality is to be rendered. It is difficult and probably impossible to practice good medicine in geographic or cultural isolation from one's peers, and certainly good medicine cannot be practiced without sufficient facilities and resources. Thus it is seen that the clustering factor, the distance factor and the cultural factor not only relate to one another but also pertain to each of the three categories of under-served just described. None has generally been taken into sufficient account in most attempts to date to reach the unreached with health care.

Elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE Noel Guillozet presents a further progress report on a medical society-sponsored program to reach the unreached with health care in a large rural area in central California. The Southern Monterey County Medical Group appears to have taken good account of the three factors described above and to have developed a working model of what can be done, most recently overcoming the cultural, distance and "cluster" barriers to establishing a community mental health program in a rural area.

—MSMW

CASE REPORTS

Refer to: Sullivan P, Brewin A: Evidence of skeletal muscle involvement in psittacosis. West J Med 121:232-234, Sep 1974

Evidence of Skeletal Muscle Involvement in Psittacosis

PETER SULLIVAN, MD
Bethesda, Maryland

AUSTIN BREWIN, MD
San Francisco, California

PSITTACOSIS (ORNITHOSIS) is a relatively uncommon systemic disease.[1] The clinical syndrome is characterized by high fever and severe headache associated with a nonproductive cough. In severely ill patients the respiratory symptoms dominate the clinical features with progressive pulmonary insufficiency. Most clinical attention has rightfully been directed to the pulmonary problems, though it has long been recognized that other organs are frequently involved.[2] A case of psittacosis with probable myositis in which, for the first time, enzyme studies were carried out to confirm the diagnosis is here reported.

Report of a Case

A 43-year-old-man was seen in the outpatient clinics at San Francisco General Hospital on March 16, 1972, for gradually increasing malaise, nausea and vomiting, elevated temperature, dry cough, fatigue, headache, and generalized myalgia that had been present for 24 hours. The temperature was 40°C (104°F), pulse rate 138 beats per minute, and blood pressure 150/100 mm of mercury. Rales were heard at the left lung base. A chest roentgenogram showed a small left perihilar infiltrate. The leukocyte count was 8,600 cells per cu mm. Viral pneumonia was diagnosed and aspirin was prescribed. During the next two days the patient improved as temperature returned to normal with relief of myalgia, diminished cough, and abatement of other symptoms. In the evening of the third day of aspirin intake, the temperature rose and the patient became extremely fatigued.

He was admitted to the hospital the next day (March 20, 1972) because of an abnormally high temperature; he did not have a headache, chest pain, muscle pain, joint pain, or dyspnea. The medical history and review of systems were unremarkable except for consumption of a moderate amount of alcohol daily for a number of years. There had been no illness among the patient's family or acquaintances. He worked as a maintenance man for a firm that serviced a number of retail stores. It was learned on the fourth hospital day that one of these stores was a pet shop that contained many parakeets. He had last worked in the pet shop approximately ten days before onset of symptoms. He had no pets at home.

Physical Examination

The patient was apparently in no acute distress. The temperature was 40.4°C (104.6°F), pulse 130 beats per minute and regular, respiratory rate 16 per minute, and blood pressure 140/100 mm of mercury. The skin was warm and dry. Palpable lymph nodes were not enlarged. The pharynx was injected without exudate. Dullness and egophony were noted in the region of the left upper lung fields. The heart was not enlarged. A grade 2/6 systolic ejection murmur was heard at the left sternal border without radiation; heart sounds were normal. There was no venous distension; peripheral pulses were intact. The abdomen was distended but there was no visceromegaly nor palpable masses. No abnormalities were detected in the genitalia, muscular-skeletal system, or extremities. No abnormalities were noted on neurologic examination.

From the Medical Service, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco, School of Medicine.

Submitted January 25, 1974.

Reprint requests to: A. Brewin, MD, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110.

Laboratory Results

Hemoglobin was 13.3 grams per 100 ml, hematocrit 39 ml per 100 ml, and leukocyte count 7,900 per cu mm with 54 percent polymorphonuclear cells, 29 percent band forms, and 17 percent lymphocytes. Platelet count was within normal limits. Serum sodium was 125 mEq, potassium 5 mEq, chloride 105 mEq, bicarbonate 25 mEq per liter, blood urea nitrogen 10 mg, and creatinine 0.7 mg per 100 ml. Serum glutamic oxaloacetic transaminase (SGOT) was 950, lactic dehydrogenase (LDH) 1,600, and creatine phosphokinase (CPK) 67,200 units, all expressed as International Units per liter. Urinalysis revealed trace ketones, 3+ protein, many hyaline casts, and occasional white and red blood cells. A Gram-stained sputum specimen showed polymorphonuclear cells with no predominant microorganisms. A chest roentgenogram showed an infiltrate in the left upper lobe. The electrocardiogram showed no abnormalities.

Hospital Course

After collection of specimens for culture, including a transtracheal aspirate, 600,000 units of procaine penicillin G was administered intramuscularly twice a day. On day 2 the temperature was 40°C (104°F), the sputum production increased and contained polymorphonuclear cells but no bacteria by smear, and an electrocardiogram again showed no abnormalities. The transtracheal culture specimen grew no organisms. On day 3 the patient began to complain of shortness of breath; a chest roentgenogram showed a dense infiltrate in the right lower lobe as well as in the left upper lobe. The temperature was still 40°C; arterial blood P_{O_2} was 46 mm of mercury, P_{CO_2} 35 mm, and the pH 7.36. Penicillin was discontinued and cephalothin, 2 grams every six hours intravenously, and kanamycin, 500 mg every 12 hours intramuscularly, were begun. On day 4 the temperature was still elevated. The SGOT was 725, LDH 970, CPK 31,200, and aldolase 56.6 units. Arterial blood gases during nasal administration of 7 liters per minute of oxygen were P_{CO_2} 30 mm of mercury, P_{O_2} 55 mm, and the pH 7.37. The patient continued to be short of breath, dyspnea occurring when he talked. He continued to cough, producing small amounts of sputum that contained polymorphonuclear cells but no organisms. At this point the history of exposure to birds in the pet shop was learned for the first time. Cephalothin and kanamycin were discontinued and tetracycline therapy, 250 mg four times a day orally, was begun. On day 5, the patient was symptomatically much improved. The temperature fell below 37.8° (100°F) for the first time; arterial blood gases while breathing room air were: P_{CO_2}, 30 mm and P_{O_2} 62 mm of mercury, and the pH was 7.40. A chest roentgenogram showed interval clearing of the infiltrate in the left upper lobe while the right lower lobe infiltrate remained stable. An electrocardiogram was still normal. The patient remained afebrile and continued to improve symptomatically. Arterial blood gases were within normal limits by day 7, and the CPK was 189, LDH 240, SGOT 140, and aldolase 8.9 units by day 8. The patient was discharged on March 30, 1972. Tetracycline therapy was terminated two weeks later. Chest roentgenogram after discharge showed no abnormalities. The patient remained free of symptoms and was healthy and working when last seen six months later.

Measurement of LDH isoenzymes in a blood specimen obtained on the second hospital day revealed an absolute increase in all fractions with a relative increase in LDH 5. The specimen run had 1,600 units total, 8 percent Fraction I, 14 percent Fraction II, 15 percent Fraction III, 14 percent Fraction IV, and 49 percent Fraction V. Specimens for serologic tests* for mycoplasma, influenza A and B, adenovirus, Q fever, histoplasmosis, blastomycosis, coccidiodomycosis, mononucleosis, and psittacosis-lymphogranuloma venereum were drawn on March 20 and again on April 17, 1972. Only the psittacosis-lymphogranuloma venereum titers, which increased from 1:8 to 1:256, were diagnostic of disease.

Discussion

Although we did not attempt to isolate the psittacosis agent, the clinical manifestations, the response to tetracycline, and the pronounced rise of the psittacosis-lymphogranuloma venereum titers from 1:8 to 1:256 over four weeks ultimately confirmed that our patient had psittacosis.[3] The source of his illness would seem to have been the pet shop where he worked; however, an inspection by the San Francisco Department of Public Health revealed no evidence of the disease in the birds or employees, and the proprietors denied any unusual illness among their birds. Therefore,

*Performed by the Viral and Rickettsial Disease Laboratory of the California State Department of Public Health.

it was impossible to establish the actual source of the illness. Of the 33 cases reported to the National Center for Disease Control in 1971, there were three in which no obvious source was identified.[1]

The most prominent system involved in patients with psittacosis is the lung; however, the systemic nature of the illness has long been recognized, and headache, malaise, and myalgia are the usual presenting symptoms.[4,5] Yow and associates reviewed the literature on the organ systems known to be involved: lungs, tracheobronchial tree, heart, liver, kidneys, brain, meninges, and spleen.[5] Myalgia was noted in 17 of the 24 patients reported by Yow et al[5] and in four of the nine patients reported by Schaffner et al,[6] and it was stated to occur "commonly" in the 29 cases reported by Barrett and Greenberg.[7] To the best of our knowledge, enzyme studies have not been carried out previously in these circumstances.

The pronounced elevation of CPK, aldolase, LDH, and SGOT in the presence of a normal electrocardiogram and normal mental status and neurologic examinations and normal levels of alkaline phosphatase and bilirubin indicates widespread involvement of the patient's muscle mass.[8] This process appeared to be self-limited, as the enzyme levels began to decline toward normal and the symptoms began to subside before tetracycline therapy was begun.

Although myalgia is common in clinical cases of psittacosis, this may also be true in less severe cases, as is suggested by the increased incidence of myalgia among members of a population exposed to birds compared with a group not so exposed.[9] The more frequent use of serologic studies in patients who have a sporadic "flu" syndrome might give a better idea of the incidence of psittacosis infections. The major clue should be exposure to birds, whether psittacine, pigeon, or fowl;[4] in such cases serologic confirmation should be obtained and tetracycline therapy considered.

Autopsy studies indicating degenerative changes of the rectus abdominus muscles in several fatal cases were reported by the British Ministry of Health following the 1929-30 pandemic of psittacosis.[10] Two additional cases were described in a report by Binford and Hauser[11] in 1944; however, we are not aware of histologic confirmation of muscle involvement having been made in any nonfatal case of psittacosis.

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LETTERS *to the Editor*

Early and Periodic Screening

To the Editor: ". . . activism without rationality, even for the noblest ideals may exploit those with the greatest problems. Funds to meet the needs of children must not be dissipated by useless screening" (Gershman M: Position on early and periodic screening (Letter to the Editor). West J Med 121:69, Jul 1974).

Right on!

I know of no practicing physician more experienced or enthusiastic about preventive examinations than myself, with about 20,000 in 20 years (4 daily) complete from diet diary and emotional evaluation of children to tonometry and sigmoidoscopy of adults over 35. Obviously, my patients and I find my examinations very productive or we would not continue them. However, I, too, would urge your readers to oppose implementation of Brown Bill AB 2068, now Chapter 1069 of the Health and Safety Code, financing health screening for Medicaid eligibles under age 21.

If politicians had done their homework (and cared about results) they would have learned from numerous studies that:

(1) The likelihood of eliciting significant health problems is much less when done in mass production than when done by the personal physician;

(2) The cost of such services is far greater when done by bureaucracy instead of fee-for-service physicians—even with competition as diluted as it is by (a) organization opposition to public information on prices and, (b) by third party payment minimizing motivation for thrift;

(3) Follow-up action on defects detected in mass screening is relatively poor, compared with correction of health deficiencies found by the family doctor.

References range from the Pennsylvania studies of the '50s (which portrayed the frustration of finding the prevalent tooth decay, occasional significant heart murmurs, etc., which were generally untreated years after discovery), to readers' own recent experience with hard-to-read computer print-outs from the Cannery Workers, to the family doctor largely duplicating Palo Alto Clinic "executive examinations," in order to properly treat his ulcer patient.

"Doctor" comes from Latin "docere" meaning "to teach." An effective personal physician spends most of his time eliciting learning. He and his aides have much better opportunity than strange clerk, piece of paper, or even Public Health nurse to adequately motivate a wheezy smoker, fat diabetic, type A hypercholesterolemic, asymptomatic rectal polyp owner, or oppressive parent.

Shall we merely establish another of the Editor's well-noted "adversary relationships" against government, where "tragically, once again it will be the patients who will inevitably bear the brunt"? Or shall we fulfill the need for personal physicians' comprehensive periodic health evaluations (yearly checkups)?

Howard F. Long, MD
Pleasanton, CA

Nocardia Asteroides Infections

To the Editor: In the recent report by Epstein [Epstein E: Treatment of cutaneous Nocardia asteroides infection with minocycline hydrochloride. West J Med 120:497-499, Jun 1974] of a patient with infection due to Nocardia asteroides, there are three assumptions that should not pass unchallenged, namely, that the infection in the patient presented was limited to the skin, that there is evidence that minocycline is effective in the treatment of nocardiosis, and that 77 days of therapy is an "extended" course for this infection.

There is little doubt that a normal chest x-ray does not rule out disseminated nocardiosis. A nocardial brain abscess and an abscess of the psoas muscle—improbable sites for direct inoculation of the organism—have been reported in two patients in whom there was no evidence of pulmonary involvement.[1] We have recently seen two heart transplant patients who also illustrate this point.[2] In one patient with nocardial subcutaneous abscesses, chest x-ray revealed a very small lesion

(possibly due to Nocardia) which, in retrospect, had been present one month earlier. The other patient died and at autopsy was found to have a small pulmonary nocardial abscess that had been clinically and roentgenographically inapparent. We consider the possibility that the patient whose metastatic skin abscess has become clinically apparent might also have a nocardial lesion growing silently in the brain.

Sulfonamides are the "classic agents" for treating nocardiosis because they are extremely effective in the great majority of patients who are not moribund due to one or more brain abscesses. However, there are patients who cannot take sulfonamides or in whom the infection does not appear to be responding to these agents. It is primarily for these reasons, as clearly stated by Bach et al,[3] that their recent paper describing the use of drugs other than sulfonamides in two patients with nocardiosis is important. In the patient of Bach et al, sputum culture became positive within 48 hours after discontinuing a two-month course of minocycline, and when the patient died from unrelated causes after another five-to-six week course of minocycline, sections of lung at autopsy disclosed organisms compatible with Nocardia. The patient described in the other paper[4] cited by Epstein had a pulmonary nocardial lesion that stabilized on nine days of intravenous sulfisoxasole therapy. Since sulfisoxasole was not discontinued when minocycline was begun, and since it is not unreasonable to expect a cavitary nocardial lesion to take more than nine days to regress, the contribution of minocycline to the course of this patient's nocardiosis is moot. We find it difficult to accept these two published cases as evidence that minocycline is effective as the sole antimicrobial therapy for nocardiosis. However, the patient of Bach et al and Epstein's patient do constitute a small amount of evidence that minocycline may be effective in the short-term suppression of this infection. Because of the proven efficacy of sulfonamides in treating this infection, we believe that the latter antimicrobial agents remain the drugs of choice for nocardiosis.

The duration of therapy necessary to eradicate a nocardial infection is not known, but relapses have occurred often enough that the importance of treatment up to or even longer than a year has become apparent.[1,5] A healthy respect for the ability of this organism to "play possum" may be acquired from the report of a patient who was in his fifth month of sulfonamide therapy for nocardial subcutaneous abscesses when he developed clinically apparent multiple nocardial brain abscesses.[6] Although it is possible that Epstein's patient was "cured" by a two and one-half month course of minocycline, such a course of therapy is not to be considered as being "extended" in the treatment of this infection. Long-term follow-up information on his patient will be of great interest.

James A. Krick, MD
Jack S. Remington, MD
Stanford

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The Author Replies

I FIND IT DIFFICULT to understand the criticisms raised by Drs. Krick and Remington. All that this article intended to do was to briefly present the case of a man on immunosuppressive therapy who developed an abscess on his leg due to N. asteroides and which cleared with the oral administration of minocycline hydrochloride. These correspondents list three objections to the presentation all of which seem to be answered in this less than monographic article.

First, they deny that the infection in this patient was limited to the skin. The only statement in this regard is, "There was no evidence of nocardial involvement of any system other than the skin." It is admitted in the article that, "Usually the lungs are the site of infection, but other organs—the skin, for example—may be involved either by dissemination or by direct primary infection." I have no evidence that any system other than the cutaneous one was involved. Perhaps Krick and Remington have more divine guidance than I do.

Secondly, they express doubt that minocycline hydrochloride is effective in nocardiosis. The article quotes a number of other investigators who agree that this agent is of benefit in controlling this infection. No one denies the efficacy of sul-

fonamides. In fact, the article states, "Although sulfonamides have been the classic agents for treating nocardial infections it is now becoming apparent that other antibacterial agents are efficacious." This hardly denies the importance of sulfonamides.

The third point concerns the length of therapy and the denial that 77 days is "extended treatment." I am unable to locate the statement "extended treatment" in the article. However, it does touch on this point by stating, "To be successful, therapy must be aggressive even to the point of extending treatment for several months to a year beyond clinical cure." The patient was seen last thirteen months after the conclusion of therapy and was still well despite the continuation of immunosuppressive therapy. This does suggest that the treatment may have been adequate.

I would appreciate further information on what factor inspired this communication.

ERVIN EPSTEIN, MD
Oakland

More on Electromyography

TO THE EDITOR: I would like to respond to a letter on who should perform electromyography, written by Nickel and Ashley [Nickel VL, Ashley EJ: On the performance of electromyography (EMG) (Letter to the Editor). West J Med 120:500-501, Jun 1974]. I should say that any rationale for nonqualified individuals to perform electrodiagnosis is difficult for me to understand. A diagnostic test on which decisions are made with respect to surgery, disability, serious prognoses and recommendations for changes in life style should be performed by the most qualified individuals possible.

The American Association of Electromyography and Electrodiagnosis, the only organization in this country exclusively devoted to promoting the technique of electromyography and electrodiagnosis, has recently adopted a resolution indicating that only a physician-specialist with additional training in clinical neurophysiology and electrodiagnosis should be involved in the performance of the test.

There is a common misconception that electromyography is similar to electrocardiography, or electroencephalography, this is—a record made by a technician and interpreted later by a physician-specialist. This is not so, since the electrical activity is dependent on the electromyographer's actions at a given moment and is not recorded. Furthermore, there are no standard leads but rather more than 400 muscles to be investigated and many accessible nerves to do nerve stimulation studies. Furthermore, the examination is planned after an appropriate history and physical examination and then modified as the electromyographic findings unfold. Such a procedure is impossible for a technician no matter how well trained to perform.

My answer to Drs. Nickel and Ashley would be *NO* test is better than a test poorly performed which may mislead the referring physician.

ERNEST W. JOHNSON, MD
Professor and Chairman
Department of Physical Medicine
Ohio State University
Columbus

* * *

TO THE EDITOR: For over twenty-five years diagnostic needle electromyography has been performed by physicians. These physicians have almost entirely been comprised of specialists in physical medicine and rehabilitation, or specialists in neurology. The standard of practice throughout the United States and California is to have diagnostic needle electromyography performed by physicians specializing in these fields.

Over these past thirty years, a tremendous amount of information has accumulated in the field of diagnostic electromyography and a specialty organization, the American Association of Electromyography and Electrodiagnosis, has been in existence for many years. Our association, the A.A.E.E., has constantly strived to improve the training of physicians performing electromyography and to promote advancements and the dissemination of knowledge in electromyography. It is our feeling that a physician practicing diagnostic needle electromyography not only must have an excellent background in neurophysiology, neuroanatomy, and kinesiology but also should have formal education and experience in skeletoneuromuscular disorders, particularly those in which diagnosis through electromyography plays an important role. Within the last two years the American Board of Physical Medicine and Rehabilitation has considered that formal training in electromyography is so important as to make it an integral part of the residency training program.

Each resident in physical medicine and rehabilitation is now required to perform and document at least 200 diagnostic needle EMG's on selected patients, under direct supervision of an experienced electromyographer.

Residents in neurology are also offered training in diagnostic needle electromyography, and many neurologists in the state of California perform this diagnostic procedure. The tremendous depth and scope of electromyography both in research and clinical applications is reflected by the three volume edition, *New Developments in Electromyography and Clinical Neurophysiology,* edited by Desmedt, published by S. Karger, 1973, to cite but one of many works in this field. A review of the table of contents of these three volumes will readily reveal the enormous scope and complexity of the field, and will quickly dispel the idea that a physical therapist can or should do diagnostic needle electromyography. I personally know of no physical therapist who does diagnostic needle electromyography but know of several who are doing electromyography using skin electrodes in kinesiological research study. The type of information in this type of study is entirely different from the kind of information received in diagnostic needle electromyography. In view of the standard of practice of electromyography in the United States and California any physical therapist doing diagnostic needle electromyography would be guilty of malpractice. With the great shortage of physical therapists available to perform the important work of physical therapy for which they were trained I find it most difficult to understand the logic of trying to divert them into a new field. The opinion of Dr. Nickel and Mr. Ashley [West J Med 120: 500-501, Jun 1974] is not shared with physicians qualified to do electromyography.

A list of qualified physician electromyographers may be obtained by writing for the directory of the American Association of Electromyography and Electrodiagnosis to Dr. W. C. Wiederholdt, secretary, 3350 La Jolla Village Drive, San Diego, California, 92161. If Dr. Nickel is unable to obtain a qualified electromyographer to perform the EMG examinations at Rancho Los Amigos, he may call me at my office (213) 542-8157. I would be happy to assist him in locating a qualified physician electromyographer.

WILLIAM J. LAJOIE, MD
Associate Clinical Professor Rehabilitation Medicine
L.A. County - U.S.C. Medical Center
Electromyographer, Orthopaedic Hospital
Los Angeles

More on Electromyography

TO THE EDITOR: Dr. Vernon L. Nickel's enthusiastic support for physical therapists performing electromyography [Nickel V, Ashley EJ: On the performance of electromyography (EMG) (Letter to Editor). West J Med 120:500-501, Jun 1974] flows from a premise that "a physical therapist is particularly appropriate to this type of examination because of his strong background in anatomy and particularly in functional anatomy which, in actual fact, often surpasses many modern trained physicians." He also states an untested conclusion that "some physical therapists have become proficient in performing EMG's."

The conclusion that knowledge of functional anatomy is sufficient a basis on which to build skill in electromyography is obviously erroneous. An electromyogram is an electrophysiological assessment of a patient's motor system and there is far more to test than looking at a few potentials published in textbooks which are increasingly under revision in this field. The training of the eyes and the ears of a physician to the artifacts that a machine produces for muscle and nerve activity takes years, despite close supervision. There is no way to satisfactorily record the study so that it can be reviewed at a later time. Like a surgical procedure, it must flow depending upon the immediate information obtained and the implications of an improperly drawn conclusion are enormous. A "sharp wave" on a report often "justifies" a sharp knife the next morning, and there is no going back.

Is it reasonable to assume that a physical therapist is only going to examine the simple cases and, in a new and delightful outlet, easily admit that he has strayed over his head? It is human that a report will be made, and reports can appear profound. The faith that can be placed in an electromyographic report depends upon the quality and demonstrated integrity of the electromyographer. It, therefore, becomes a matter of conscience when a physician refers one of his patients to another for an answer from which he will possibly undertake hazardous acts.

The issue may come into better comparative perspective if each physician would consider if he would permit his patients to undergo contrast

study radiologic examination under fluoroscopic control by a "specially trained" x-ray technician. At least in that case, there will be some degree of relevant permanent documentation. Further, would Dr. Nickel advocate specially trained technicians performing some of the "simple" orthopedic surgical procedures that take 10 to 15 minutes? Does it take the availability of all the training of an orthopedic surgeon in each instance? Is it a specialized physician performing an electrophysiological or a surgical dissection who is more likely to perform well, commensurate with his responsibility, or a specially trained non-physician without the broad knowledge and experience necessary to the instance. Dr. Nickel further admits the shortage of qualified electromyographers at Rancho Los Amigos; who, therefore, would supervise the examination, and where would the extensive training be obtained?

The questions raised are to a purpose but irrelevant. Dr. Nickel suggests establishing precedence in the courts by stating that electromyography is already being done by physical therapists. I would urge that the California State Code concerning the practice of physical therapy be consulted. It is not permissive and a privilege unstated cannot be construed. Physical therapists are not permitted to enter the body with needles. This is not a civil matter for adjudication but a criminal one, a misdemeanor assault. Such an admission of previous commission of an unlawful act does not seem to me to be advantageous defense, and any complaint would require a criminal investigation by the Department of Consumer Affairs. If the Code were at some time changed, there would still be the inevitable court challenge of a conflict of expert testimony. How, then, would a physical therapist stand against an experienced physician?

I am, and will continue to be, a supporter of the development of enlightened and proficient physical therapy in this country, and there is now the beginnings of an effort within the American Physical Therapy Association to revise curricula so that American therapists will be as well trained as their colleagues from the United Kingdom and Scandinavia. The dominance of academics and machines in American training has cost them the loss of irreplaceable manual skills which, in my opinion, must be replaced and should be first priority. To my knowledge, only a few therapists are interested in electromyography.

I regret the shortage of qualified electromyographers at Rancho Los Amigos, but physiatry has been discouraged there, and they are one of the only two specialties trained in it.

PAUL H. GOODLEY, MD
Resident
Department of Physical Medicine and Rehabilitation
University of California, Davis, Sacramento Medical Center
Sacramento

Trauma Rounds

Chief Discussant
MURIEL STEELE, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Steele M: Management of pancreatic injuries (Trauma Rounds). West J Med 121:240-243, Sep 1974

Management of Pancreatic Injuries

JOHN WILSON, MD:* A 17-year-old boy received a blow to the head and a steering wheel injury to the abdomen in an automobile accident. When admitted to the Emergency Room he was complaining of abdominal pain. He responded to questioning but was restless, agitated and combative and was thrashing about wildly.

On physical examination blood pressure was 125/70 mm of mercury with a pulse rate of 110. He had multiple facial lacerations which were bleeding profusely, and a contusion about the left eye. He was able to take a deep breath without apparent discomfort. The lungs were clear and the abdomen was relatively soft but difficult to evaluate because the patient would not hold still during the examination. Peripheral perfusion seemed adequate although the extremities felt a bit cool.

Tubes were placed in the basilic and greater saphenous veins and a Foley catheter was inserted into the bladder. The hematocrit was 41 percent. The urine was clear. Cervical, skull, chest and abdominal x-ray films were considered normal.

Approximately two liters of Ringer's lactate solution was infused within one hour after entry. The blood pressure had remained stable at 120/70 mm of mercury but the hematocrit had fallen to 33 percent. The abdomen did not change appreciably although there appeared to be slight spasm of the upper abdominal muscles. Two hours after admission the urinary output dropped to 20 ml per hour and blood pressure fell to 85/40 mm.

At laparotomy, a liter of blood was found in the abdominal cavity, most of it coming from a rupture of the spleen. On examination of the lesser sac a complete fracture of the body of the pancreas and a mesenteric hematoma were noted. The spleen was removed in continuity with the distal portion of the pancreas. The pancreatic duct was identified in the proximal portion of the divided pancreas and was suture-ligated. Tubes were placed in the left flank to drain the pancreatic bed. The patient received 5 units of packed cells and 3 liters of crystalloids during operation.

Postoperatively the blood pressure was normal and the hemocrit was 41 percent. Urinary output was excellent. The patient remained confused, combative and somewhat disoriented, but his mental status gradually returned to normal over the next several days. At the time of this report, one week after injury, he was alert and oriented. The drains had not been removed but otherwise he was ready for discharge.

DONALD TRUNKEY, MD:† I would like to mention that when this patient first came into the Emergency Room he was described as restless and agitated. Such behavior might be attributable to

*Trauma Service Intern.

Sponsored by The American College of Surgeons Northern California Trauma Committee. Supported in part by NIH Grant GM18470.

†Chief of Surgery, Mission Emergency Hospital and Assistant Professor of Surgery, University of California, San Francisco.

a head injury or to the taking of drugs or ingestion of alcohol, but these findings can also be due to severe hypovolemia. In these circumstances, it is up to the emergency room physician to prove that it is not hypovolemia by monitoring peripheral perfusion (skin temperature) and urinary output.

Dr. Steele,* you have been personally responsible for the management of many of these pancreatic injuries and have recently reviewed the experience at San Francisco General Hospital. Will you comment on the management of this particular patient and pancreatic injuries in general?

DR. STEELE: It was stated at the onset that this patient had a steering wheel injury to the epigastrium. Any patient who has an injury of this type is at risk of damage to the liver, the spleen and, in particular, the pancreas. This is the typical mechanism for production of a pancreatic rupture. The pancreas fractures over the vertebral column when the epigastrium is crushed against the steering wheel of a car. Liver and spleen injuries produce manifestations of hypovolemia, and the splenic injury in the case we are discussing might even be considered fortunate, since it led to the early diagnosis of the pancreatic injury. Pancreatic injuries are notoriously diagnosed late because damage to this retroperitoneal organ often does not produce much in the way of abdominal findings. Typically these patients have abdominal pain which may be out of proportion to the clinical findings. Therefore, a blow to the epigastrium combined with epigastric pain and even minimal epigastric tenderness should lead to a high index of suspicion of pancreatic injury; and it indicates the need for laparotomy. A high leukocyte count and abnormal serum amylase content tend to support the diagnosis, although normal amylase content does not rule out injury.

The primary problem in pancreatic trauma once laparotomy is carried out is assessment of the injury. In this particular patient the injury was obvious. The pancreas was fractured in the typical location right at the neck where the pancreas passes over the vertebral column. This patient also had considerable hematoma in the mesocolon, which pointed to the injury. The proper treatment was carried out and the patient should do well. There is a fair chance that he will have a temporary pancreatic fistula but this should be benign, as it is unlikely the proximal portion of the duct was damaged by the injury.

In the average case, assessment of the degree of injury to the pancreas is the primary problem. Penetrating injury is not difficult to assess, for major disruption of the gland is apparent. Penetrating injuries of the body or tail are best treated by distal resection. Injuries to the head will be described later.

Assessing blunt traumatic injury is more difficult. In any case of upper abdominal injury the pancreas should be systematically explored at the time of laparotomy. This should be done by a specific routine. Initially the transverse colon and omentum should be elevated superiorly and the retroperitoneum inspected in the vicinity of the ligament of Treitz and around the root of the mesocolon. The presence of blood, induration or saponification is suggestive of pancreatic injury. Next, the anterior surface of the pancreas should be inspected. This requires entering the lesser sac. The most appropriate way to enter the lesser sac is by detaching the omentum from the colon so as to avoid dividing gastroepiploic vessels and devascularizing the greater curvature of the stomach. Although in normal circumstances the stomach has good blood supply, the combination of injury and shock may produce intense splanchnic vasoconstriction so that interruption of any portion of the blood supply of the greater curvature may aggravate ischemic damage to the stomach and set the stage for subsequent "stress ulceration."

Upon opening the lesser sac, gentle retraction of the stomach permits inspection of most of the anterior surface of the pancreas. If there is hemorrhage over the gland, then the tail along with the spleen should be mobilized upward to the right to permit inspection of the posterior aspect of the body and tail and careful bimanual palpation of the gland to determine its integrity.

Next, the retroperitoneum is inspected just lateral to the duodenal sweep. If there is hemorrhage around or lateral to the duodenum, a Kocher maneuver should be carried out and the head of the pancreas inspected posteriorly and palpated bimanually. Without careful palpation of areas which appear to represent trivial injuries, it is difficult to recognize the full extent of the problem. All too often the hematoma will smooth out the anatomic structure so that unless it is palpated carefully, the full magnitude of the disruption of the gland is not ascertained.

If the integrity of the pancreas seems relatively

*Muriel Steele, MD, Associate Clinical Professor of Surgery, University of California, San Francisco and Assistant Chief of the Surgical Service, San Francisco General Hospital.

normal, drainage is carried out. If the integrity of the gland is compromised, distal resection is indicated, assuming the area of injury involves the neck, body or tail as is the case with most blunt injuries. In approximately 50 percent of our patients with pancreatic injuries resection is required, and the remainder are managed by drainage.

When the injury involves the head of the pancreas, one method of management is the Whipple procedure. In most series, including our own, this results in an unacceptably high mortality and morbidity, and its use should be limited to extensive disruptions of both the head of pancreas and the duodenum, such as are occasionally produced by gunshot wounds. A better alternative, when the injury is extensive but limited to the head of the pancreas, is to carry out an extensive distal resection leaving enough pancreas to preserve the blood supply of the duodenum. For the combined pancreaticoduodenal injury, diversion of gastric contents from the duodenum with repair and drainage of the injured areas as described by Byrne may be appropriate; and this procedure provides a better chance of survival from these potentially lethal injuries. The operation includes resection of the antrum of the stomach and a gastrojejunostomy. This converts the duodenum into a conduit limited to bile and pancreatic juice. By separating the gastric contents from the pancreatic enzymes, activation of the latter is avoided along with many of the hazards of digestion of suture lines and upper abdominal structures. In the few instances we have used this procedure it has worked very well and is much better tolerated by patients with multiple injuries. Patients who have the duodenal diverticulization should also have vagotomy. This puts the pancreas at rest and lessens the risk of "stress ulceration" of the stomach.

On the rare occasion in which you are forced to do a Whipple operation, I do not believe you should attempt to reimplant the distal end of the pancreas into the gastrointestinal tract. You should either ligate the duct and drain it in an attempt to preserve endocrine function, or resect the pancreas totally, to avoid the possibility of adding a pancreatic fistula to the patient's problems. Patients with complicated injuries do poorly, and physicians treating them should accept the morbidity of total pancreatectomy to preserve life.

In all pancreatic injuries, drains should be placed whether or not resection has been carried out. Large Penrose drains with or without a sump drain should be inserted in the pancreatic bed or over the area of injury. These should be brought out the flank in as dependent a position as possible.

A Physician: *If there is questionable damage to the duct, is that an indication for some type of pancreatography or re-exploration at a later date?*

Dr. Steele: I would be opposed to the latter. Twenty-four hours after injury the pancreas is a greater problem to deal with than it was initially. If the patient's pancreas had been slightly injured, there is often considerable inflammation around the gland 24 hours later, making it very difficult to assess. As to whether or not we can endoscopically cannulate the pancreatic duct for pancreatography, we still have not reached the point clinically where this is readily done and is practical. As our experience with pancreatography increases, this may prove to be a practical clinical adjunct. In the normal gland, the distal portion of the duct is difficult to identify. I do not believe you should go so far as to open the duodenum to cannulate the pancreatic duct because then you create the potential for a combined pancreatic and duodenal fistula.

A Physician: *Is there any justification for attempting to salvage the distal pancreas when the gland is completely divided, as it was in this case today?*

Dr. Steele: Patients tolerate distal pancreatectomy well, and if as much as 20 percent of the pancreas is preserved, there is little chance that endocrine or exocrine deficiency will result.

The primary risk in all pancreatic injuries is the development of a pancreatic fistula. The overall mortality from pancreatic injuries is 20 percent and about half the survivors have serious complications. Approximately two-thirds of patients have serious associated injuries, which are the usual cause of death. At San Francisco General Hospital, you would have to go back about 15 years to find a death from a solitary pancreatic injury. Complications are frequent and involve about 50 percent of the patients. These are related mainly to pancreatic fistula or to subphrenic infections. At the San Francisco General Hospital, our mortality is running about 16 percent.

Dr. Trunkey: Let me summarize the presentation by Dr. Steele as follows:

Signs of pancreatic injury are often subtle; and clinical recognition may be difficult. Whenever

there is history of major blunt trauma to the epigastrium, particularly a steering wheel injury, the possibility of pancreatic injury is real. The patient often has abdominal pain out of proportion to the physical findings. Elevation of serum amylase content or a rising leukocyte count may be clues to the injury.

At laparotomy, systemic exploration of the pancreas is indicated. This requires inspection of the base of the mesocolon around the ligament of Treitz, opening the lesser sac, inspecting the anterior surface of the gland and examining the area around the duodenal sweep. The presence of blood requires further assessment which includes a Kocher maneuver to inspect and palpate the head of the gland if there is hematoma around the duodenum, or mobilization of the body and tail should evidence of more distal injury be present.

Disruption of the integrity of the gland should be treated by distal resection for injuries of the body or tail. Major disruptions of the head of the gland, in the absence of duodenal injury, can be treated by radical distal resection. If the injury involves the duodenum, gastric diversion should be considered, utilizing distal gastric resection with gastroenterostomy combined with vagotomy. Only in the presence of severe devascularizing injuries of the head of the pancreas and the duodenum should a Whipple resection be considered. Drainage should be used routinely in all pancreatic injuries whether or not resection is carried out.

Epilepsy and Intercourse

MOST ADOLESCENTS who are epileptic are extraordinarily preoccupied with whether or not they will have a seizure while having intercourse. If you think about it, most post-pubertal youngsters are extremely interested in sexuality and "when is it going to happen to me?" The epileptic adolescent, of course, gets highly preoccupied as to whether he will, as it were, lose control during the sex act. In my clinical experience, it's rare indeed that this is an issue that's ever discussed with them. I used to be able to feel comfortable, actually, that one could be quite flatly reassuring with youngsters, because it never happened. But, regrettably, it does, because I saw a young man the other day who, in fact, did have a grand mal seizure while having intercourse.

—DEREK MILLER, MD, *Ann Arbor*

Extracted from *Audio-Digest Psychiatry*, Vol. 3, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Kohlman RJ: Malpractice liability for failing to report child abuse (Medical Jurisprudence) [Reprinted from Calif State Bar J 49:(2)118-123; 184-185, Mar-Apr, 1974]. West J Med 121:244-248, Sep 1974

Malpractice Liability for Failing to Report Child Abuse

RICHARD J. KOHLMAN, Esq., *San Jose*

EVERY YEAR IN CALIFORNIA an estimated 20,000 children are physically assaulted and battered by parents or custodial caretakers. Most of these children are under the age of three years. The level of abuse inflicted upon them is sufficient to require medical treatment in the majority of cases. Tragically, fully one-fourth of them will suffer serious permanent injury or death as a result. These are not "sexually molested" children. They are not "abandoned or neglected" children. Rather, they comprise a separate and identifiable category of minors called "battered" children; their affliction—the "battered child syndrome."

Child battering occurs when an infant's foot or arm is twisted into a fracture; when a baby is picked up by the heels and smashed into a wall; when it is punctured with pins and needles; when it is burned with cigarettes; when its hand is held under an open hot water tap or its foot immersed in a tub of scalding water; when it is viciously punched, poked, whipped or beaten.

Syndrome

In 1962 Dr. Henry Kempe of the University of Colorado Medical School coined the term "battered child syndrome" in his landmark article in the Journal of the American Medical Association.[1] This paper was the culmination of approximately twenty years of investigative medical research by his group and others initially prompted by the development of x-rays and the early interest of pediatric-radiologists in the phenomenon of unexplained multiple skeletal fractures in small children. Dr. Kempe and his collaborators proved that the syndrome has human origin and established the condition as a clinical diagnosis. Moreover, they concluded that proper medical management required reporting the abuse to police and juvenile authorities for follow-up investigation and protective custody for the battered child in appropriate cases. "All too often," they found, "the child returns to his home only to be assaulted again and suffer permanent brain damage or death."[2]

Clinical symptoms of the disease include subdural hematoma (an accumulation of blood within the cranium between the brain and its outer lining, often caused by a blow to the head) in a large percentage of cases. Similarly, in many instances, fractures of an unusual nature (*e.g.*, lower leg spiral fracture in a child too young to walk) constitute the principal complaint given the examining doctor. In most cases, there is an attendant galaxy of bruises, punctures, bites and burns. The major diagnostic feature of the battered child syndrome is a marked discrepancy between the clinical findings and historical data supplied by the parents. Therefore, a complete skeletal x-ray examination is a standard and required part of every work-up. Where it discloses

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[1]Kempe, Silverman, Steele, Droegermueller & Silver, *The Battered Child Syndrome,* 181 JAMA 17 (1962).

[2]*Id.* at 24.

previous fractures in various stages of healing, the diagnosis will be confirmed in virtually every case. "To the informed physician," Dr. Kempe warned, "the bones tell a story the child is too young or too frightened to tell."[3]

Legislative Response

Concern for the plight of the battered child spread across the country at an unprecedented rate in medical, legal and social work circles following the publication of Dr. Kempe's article and a symposium on the subject at the Children's Bureau of the Department of Health, Education and Welfare in Washington, D.C. As with venereal disease, the treatment of the battered child syndrome is relatively simple. The principal problem is *finding* the victim. It was immediately recognized that doctors, especially pediatricians, orthopedists, radiologists and emergency room physicians, are in a singularly strategic location to sort out and identify children afflicted with the disease.

To give impetus and sanction to the recommendations of the clinical investigators that suspected incidents be reported to authorities, the legislatures of all states passed child abuse reporting statutes within three years of the publication of Dr. Kempe's paper. Not surprisingly, California led the way.[4] Based primarily on a model statute drafted and promulgated by the Children's Bureau, child abuse reporting laws require physicians and other designated persons to report to police and/or juvenile authorities all suspected incidents of physical abuse of a child brought to them for examination or treatment. In most states positive diagnosis is not required. In California, for example, it need only *appear* to the doctor "from *observation* of the minor that the minor has physical injury or injuries which *appear* to have been inflicted upon him by other than accidental means by any person."[5]

The physician is only required to report. He then treats the injury itself, which is really a symptom of the underlying disease or syndrome. In every case, he is afforded immunity from civil liability for reporting. Conversely, in most states it is a misdemeanor to *fail* to notify the appropriate authorities.[6] Finally a central report registry is established in most jurisdictions to record and later retrieve reports of incidents to the same child or its siblings. This is necessitated by the inevitable recurrence of undetected parental abuse and by the tendency of abusing parents to seek medical treatment from different doctors and hospitals on subsequent occasions.

Discouraging Aftermath

Like most legislation, the child abuse reporting statutes have failed in practice to provide the deserved measure of prevention and cure. This disappointing performance has continued notwithstanding the enormous assemblage of legal and social services marshalled to respond to reports of child battering.

The problem is simply that few doctors bother to notify officials of battered children as required by law. In 1970, Dr. Vincent J. Fontana, another pioneer in this field, wrote dejectedly, "Unfortunately, however, these laws have done little to stem the increase in the maltreatment of children and have not effectively lessened the plight of the abused and neglected child."[7] In 1967 a survey of 450 physicians most likely to come in contact with abused children[8] disclosed that one in four *would not report* a given case of suspected battered child syndrome. One in five stated that they "rarely or never" considered abuse when treating an injured child. Over half did not know the correct reporting procedure to follow in their communities.

Disbelief

There are many reasons why a large number of physicians will not report the battering inflicted on their young patients. For some, parental abuse is simply unbelievable. Others fear—unjustifiably—that criminal or civil liability may result from reporting. Many doctors do not want to seem "officious intermeddlers" to angry parents. A number misplace their duty of confidentiality with the parents instead of the child. Some physicians cynically regard legal and social agencies as ineffective to treat the problem and therefore withhold cooperation. Many simply do not want to get involved with lawyers and the courts. Of course, there is also a large group of practitioners who worry over the consequences to their private medical practices that might result from reporting. Whatever the reason, the effect is that a majority of battered children treated by doctors and hos-

[3] *Id.* at 18.
[4] Penal Code §11161.5.
[5] *Ibid.* (Emphasis added).
[6] Penal Code §11162.

[7] Letter to the Editor, 46 J. Ped. 318-319 (1970).
[8] Silver, Baren & Dublin, *Child Abuse Laws—Are They Enough?* 199 JAMA 101 (1967).

pitals are returned to their abusing custodians who, predictably, inflict further injury upon the unfortunate infants. It is doubtful that a battered child who is the subject of two hospital admissions will ever survive to a third.

The criminal sanction of the reporting statutes seems ineffectual largely because these laws are rarely enforced. There are no reported cases annotated under the California Child Abuse Reporting Statute, and shepardizing the code section will not disclose any. Furthermore, although inquiry has been made by the writer, no instances of a criminal prosecution for failure to report a suspected case of child battering are known. The criminal process has not responded well to the problem of the battered child; only private damage actions against non-complying doctors and hospitals can give the child abuse reporting statutes the desired prophylactic effect.

Theories of Civil Liability

Where failure to report a suspected incident of child battering results in further infliction of maltreatment by the abusing custodian, civil liability can be predicated on three separate bases: (1) common law medical negligence, (2) violation of the specific child abuse reporting statute (Penal Code §11161.5), and (3) violation of the general reporting statutes (Penal Code §§11160, 11161). There is a certain amount of overlapping among these theories, but each is important for a different reason.

The scope of this article will not permit an extended explication of the highly complicated problems of proximate causation, foreseeability, intervening causes, and statutory interpretation and reconciliation which a case of this type necessarily involves. However, an attempt will be made to provide the practitioner with a basic theoretical framework from within which to make a preliminary evaluation of potential cases of malpractice liability for non-reporting of child abuse. Moreover, the annexed bibliography provides selected references as a starting point for the extensive medicolegal research required to prepare and try this type of litigation.

California Recognition

Malpractice liability for negligently failing to diagnose a case of the battered child syndrome is substantially easier to establish in California than in other states because the affliction has already been judicially recognized in this state "as an accepted medical diagnosis."[9] This holding is very important because the syndrome remains unlisted in most medical indices and lexicons, and there is a large group of physicians still ignorant of its existence. Since child abuse is a judicially recognized medical diagnosis here, the undetected battered child case is essentially similar to other cases of malpractice liability for a missed diagnosis. In each case the plaintiff must prove the existence of the patient-physician relationship, the presence of symptoms of the syndrome, the failure to diagnose and the lack of treatment causing further injury or death.[10]

The failure properly to diagnose the battered child's disease presents no unusual problems of proof. An incorrect analysis of the condition may often result from not ordering a skeletal or "long-bone" x-ray examination.[11]

A subtle distinction, however, must be made respecting lack of treatment. The disease which goes uncured is the battered child syndrome, *not* the symptomatic injury—the subdural hematoma, spiral leg or arm fracture, or soft tissue injury—which occasions the visit to a doctor. Moreover, treatment of the underlying disease must include disclosing the problem to local police and juvenile departments. National medical authorities are uniform in agreeing that reporting is part of proper medical management.[12] Furthermore, statutes in most states require reporting in cases where there are fewer of the clinical signs than are necessary to establish the medical diagnosis. Such laws provide important assistance to plaintiffs, since the consensus standard in many localities may actually be *not* to report. A medical expert who so testifies, therefore, exposes his colleagues to the argument that the standard of doctors in that community is to disobey the law. Accordingly, the existence of the statute will severely inhibit the defense on this issue.

Non-Statutory Theories

However, reliance should not be placed entirely on the reporting statute. An attempt should be made to establish the standard of care independently, in order to guarantee availability of

[9] *People* v. *Jackson*, 18 Cal.App.3d 504, 507.

[10] See generally, *Stafford* v. *Schultz*, 42 Cal.2d 767; *Guilliams* v. *Hollywood Hospital*, 18 Cal.2d 97; *Cullum* v. *Seifer*, 1 Cal.App.3d 20.

[11] *Lashley* v. *Koerber*, 26 Cal.2d 83; *McBride* v. *Saylin*, 6 Cal.2d 134.

[12] Kempe, et al. n.1 at 23-24; Fontana, Donovan & Wong, *The "Maltreatment Syndrome" in Children*, 269 New England J. Med. 1389, 1392-1394 (1963); American Academy of Pediatrics, Committee on Infant & Pre-School Child, *Maltreatment of Children; The Physically Abused Child*, 37 J. Ped. 377, 379 (1966).

insurance coverage. Malpractice insurance usually does not cover liability for willful misconduct.[13] While the rule is said to be that violation of a statute will not be deemed to constitute willful misconduct in the absence of other circumstances,[14] a forty year old Court of Appeal case upholding a denial of liability insurance coverage for a plaintiff's judgment based on a violation of a statute in a medical malpractice case still stands.[15] For the same reason, allegations of malice and claims of punitive damages should be discarded. They often work against the plaintiff in a medical negligence trial anyway.[16]

The common law medical negligence theory is also necessary to widen the scope of potential defendants to include hospitals, other agencies and their employees. Reporting statutes apply only to certain enumerated individuals; and in many cases the range of the statute may prove insufficient to establish vicarious liability of an employer. Registered nurses, for example, are mandated to report under the California law only when employed by a public health agency or school district, and even then only when no doctors are present. The common law duty may be stricter, however, requiring a registered nurse in a hospital pediatric ward to report, and subjecting her employer to vicarious liability if she fails to do so.

Although non-statutory theories thus are valuable, recovery based on violation of the specific reporting statute has five principal advantages. First, an actual diagnosis of the syndrome is not required. The statute only requires that it *appear* to the physician *from observation* that the child has a non-accidental injury inflicted by another person. The latter element is necessary to exclude injuries caused by natural forces or animals. Second, even the existence of the patient-physician relationship is, strictly speaking, unnecessary. The statute covers "any case in which a minor is *brought* to a physician and surgeon, dentist, resident, intern, chiropractor, . . . for diagnosis, examination or treatment" as well as those cases where "the minor is *under* his charge or care."[17]

Third, the duty to report is created by statute and applies statewide. Trial counsel, therefore, can prepare his case without regard to the standard of the particular community or whether the trial judge will strictly apply the locality rule. For this reason, expert medical opinion testimony probably is not required to permit jury consideration in an action based on statutory violation. This is peculiarly a rule in malpractice and professional liability cases, yet the statute, by its terms, applies to religious practitioners, school superintendents and principals, county welfare department directors, and other nonmedical persons.

The final advantage, of course, is the benefit of the presumption of negligence which violation of the statute raises, although in most cases the presumption would also apply under the common law theory. The prerequisites to raising the presumption are set out in Evidence Code §669. Generally speaking, it will arise whenever the evidence supports a finding that the defendant violated a statute which caused injury or death to a member of the class of persons protected by the statute, and the harm is one which the statute was intended to prevent. While there are, as yet, no published decisions holding that non-compliance with a child abuse reporting law gives rise to a private cause of action, the general principle of recovery for statutory violations is well established in California.[18] There are also analogous decisions from other states supporting plaintiffs' recoveries in medical malpractice cases involving non-reporting of diseases in violation of statute.[19] Problems of proximate causation, however, which are not insubstantial in these cases, are the same as under the medical negligence theory.

A Third Theory Available

The third theory of recovery which should be explored in a child abuse case is the violation of the general reporting statutes which are set forth in California Penal Code §§11160 and 11161. These statutes require doctors *and hospitals* to notify the police authority whenever any person is brought to them suffering from a gunshot or knife wound "or in any case where injuries have been inflicted upon any person in violation of any penal law of this state." These statutes are construed broadly to include within their scope all injuries commonly associated with criminal acts likely to come to the attention of a hospital or

[13]See Insurance Code §533.

[14]*Schwalbe* v. *Jones*, 35 Cal.App.3d 214, 218.

[15]*Glesby* v. *Hartford Accident & Indemnity Co.*, 6 Cal.App.2d 89.

[16]See *e.g.*, *Ebaugh* v. *Rabkin*, 22 Cal.App.3d 891.

[17]Penal Code §11161.5. (Emphasis added)

[18]*Vaseley* v. *Sager*, 5 Cal.3d 153; *Brockett* v. *Kitchen Boyd Motor Co.*, 24 Cal.App.3d 87. See also *Stevens* v. *Parke Davis Co.*, 9 Cal.3d 51; *Solgaard* v. *Guy F. Atkinson Co.*, 6 Cal.3d 361; *Haft* v. *Lone Palm Hotel*, 3 Cal.3d 756; *Cf. Maloney* v. *Rath*, 69 Cal.2d 442; *Clark* v. *Dziabas*, 69 Cal.2d 449.

[19]*Medlin* v. *Bloom*, (Mass. 1918), 119 N.E. 773 [Birth defect]; *Jones* v. *Stanko*, (Ohio 1928), 160 N.E. 456 [Smallpox]; *Dietsch* v. *Mayberry*, (C.A. Ohio 1942), 47 N.E.2d 404 [Birth defect].

physician.[20] Where abuse of infants has occurred, there has been a violation of the criminal law whether it is a battery, assault with a deadly weapon, criminal neglect or abandonment, willful inflicting of cruelty or traumatic injury, or murder.[21]

The advantages of proceeding under the general reporting law are twofold: (1) the statute probably covers cases of criminal neglect or abandonment where psychic or nonphysical injury results as well as those instances where physical battering occurs; and (2) its terms include "hospitals and pharmacies," thus extending the advantages of a statutory violation cause of action against corporate medical entities. These differences in scope between the general reporting statutes and the child abuse notification law probably forestall any holding that the more specific provisions of the latter section supersede the requirements of the general legislation.

The disadvantage of a cause of action based upon violation of the general reporting statutes is the greater burden of proving the infraction. The plaintiff must show that the injury had been inflicted with one of the weapons specified in the statute or that the harm was otherwise perpetrated in violation of a penal law, and that this was known or should have been known to the defendant. Thus, the plaintiff must establish that defendant was presented with an injury which had a criminal as well as medical etiology.

Society's Benefit from Liability

A real need exists in this country to stimulate more consistent and frequent reporting of physical abuse to children. Child battering has reached truly epidemic proportions. Moreover, recent psychological studies of abusive parents and custodians disclose that most were themselves abused and battered children.[22] Each act of abuse, therefore, has within it the seed of further maltreatment of children yet unborn.

The cure of the syndrome is protection for the innocent victim and psychological treatment for his tormentor. Recurrent abuse, the hallmark of the disease, can only be prevented by disclosure and identification of the battered child. He must be sought out. He cannot speak for himself. Without minimizing the necessity for every citizen to report incidents of child abuse, doctors and hospitals are particularly skilled and strategically located to accomplish the enormous task of locating and identifying this growing group of suffering children. All necessary diagnostic tools are available. Civil and criminal immunity is accorded those who report. Legal and social units are trained and ready to respond to incident reports. But complete cooperation of doctors and hospitals is lacking; and, regrettably, the only sanction left to compel it is the imposition of civil liability.

[20]36 Ops. Atty. Gen., 200, 203 (1960).

[21]Penal Code §§242, 245, 273a, 273b, 187.

[22]Kempe, et al. n.1 at 18; Fontana, *Somewhere A Child is Crying* (Macmillan 1973) p. 57; Steele, *Violence in Our Society*, 33 The Pharos of Alpha Omega Alpha 42, 44 (1970).

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Refer to: Guillozet N: Group practice approach to rural community mental health (The Health Care Team). West J Med 121:249-253, Sep 1974

Group Practice Approach to Rural Community Mental Health

NOEL GUILLOZET, MD, *King City, California*

Confronted with the inability to offer access to trained mental health personnel to their remote rural community, a private medical group practice in California recruited and integrated psychiatric social workers in their clinic. The rapid acceptance of these newer mental health professionals by community members of all economic levels and by group physicians confirms the success of this program, now in its fourth year, and rising community interest in mental health services.

The group practice prototype affords a unique opportunity for innovation in community health care delivery in outlying areas with their traditional difficulties in attracting health care professionals.

IN RURAL AND OUTLYING AREAS, the struggle to provide acceptable levels of mental health counseling may demand more effort than is required to supply acceptable basic medical care. The distributional problems are more severe with psychiatric care manpower than with primary care physicians. Among 255,000 non-federal practicing physicians in 1970, there were 16,500 psychiatrists rendering patient care.[1] In 1969 a National Institute of Mental Health (NIMH) survey disclosed that in excess of 96 percent of non-federal psychiatrists practice in urban areas.[2] An estimated 6,400 practicing clinical psychologists and 4,400 counseling and school psychologists[3] were primarily urban-center based.

Rural areas rarely have a tradition of locally available outpatient social and mental health services. Notwithstanding the availability of funds from state as well as federal sources in many instances, rural communities rarely demand these services that are traditionally available to urban areas. More than one-fourth of the nation's population resides in towns of under 2,500.[4] This significant minority shares the stresses of the American population as a whole and bears its share of disrupted marriages and family dissolution. Indeed, rural areas have an unusually high proportion of low income residents as well as the special problems of agriculture-based economics during times of rapid inflation. Rural communities are

The author is a former director of The Rural Health Project, Inc., and consultant to The Southern Monterey County Medical Group, King City.

Reprint requests to: N. Guillozet, MD, c/o Lee Roberts, Administrator, The Southern Monterey County Medical Group, 210 Canal St., King City, CA 93930.

exposed to urban communication media and show increasing interest in receiving all manner of proffered medical and social services.[5]

What alternatives are open to rural areas for the development of mental health services? How can rising expectations and needs be met? To what mental health services should priority in development be accorded? Can a predominantly urban-centered manpower pool be utilized? The purpose of this communication is to discuss the difficulties of organizing effective and accessible mental health services in rural communities, and to report an approach that has been successful in one isolated rural community.

A Rural Mental Health Strategy

An experiment intended to explore community interest in and acceptance of a county mental health program was undertaken in southern Monterey County, California, in 1970. The goal was the provision of locally accessible counseling services of the most commonly needed variety to community residents who might seek them at some time during their life. It was anticipated that the main needs would be for counseling in acute situational crises, long-term adjustment difficulties, psychosomatic complaints and assistance with childhood and adolescent adjustment problems. The current national thrust toward community mental health programs in which the absorption into a community of the more deeply disturbed or heavily medicated patients who were previously treated in institutions was not a consideration of this program.

The participants were a rurally based private group medical practice, a county health department and a federally funded agency delivering care to the low income members of a rural agricultural community. The service area of the medical group and federal agency was approximately 2,000 square miles, twice the size of Rhode Island, with a population of approximately 25,000 of all economic levels. The center of the area was King City, a town with a population of 3,700, with the traditional deficiency of community mental health services which marks isolated rural areas. The existent medical strengths of the community were a long-established and stable medical group practice incorporating all of the community's ten resident physicians and an adjacent hospital. There were nine additional regularly scheduled clinical specialty providers, and attempts had been made at intervals to incorporate a psychiatric consultant. For a number of reasons, the outcome was disappointing and further attempts to recruit and retain a psychiatrist were discontinued.

The single alternative course for outpatient mental health counseling other than by the group's physicians was referral to two private psychiatrists or to the county's Mental Health Services Department 50 miles distant. Even when not openly resisted, these referrals made to facilities outside were associated with a high failure rate. Efforts were made to assess the reasons. There was the traditional patient unwillingness to acknowledge the need for mental health services. The distance of sources of care was an obstacle of varying severity for most community members for a first appointment. Return appointments were uniformly difficult to accomplish for persons of all economic sectors. For many patients a further difficulty was the lack of Spanish-speaking personnel in distant county Mental Health Services offices. A number of economic deterrents, both direct and indirect, were encountered.

As there was some evidence of urban oversupply of newly trained psychiatric social workers, a decision was made to test their acceptance by the community on a physician-referral basis within the medical group clinic. It seemed possible that there might be less patient reticence to accept the services of a non-psychiatrist than of a psychiatrist for counseling. Previous group experience with psychiatrists seemed to show that the clinical expectation of a psychiatric social worker might permit him greater flexibility in meeting a variety of anticipated counseling problems with patients of varying age and cultural backgrounds and with little previous experience with formal mental health counseling of any type.

The Psychiatric Social Worker in Private Medical Group Practice

Physician reluctance to accept new personnel in face-to-face patient care for what had been traditionally physician-rendered services was an initial concern. However, the host medical group of family practitioners and consultants had already gained considerable experience in accepting nonphysicians in a variety of traditional roles. A Home Health Care Agency had successfully used an extended care nurse for several years.[6] A physician's assistant had once been utilized by the group and a pediatric nurse practitioner had been well accepted during two and a half years of working with the group's physicians.[7,8] Additionally, an

obstetrics nurse practitioner program had recently been initiated to assist in antenatal and postpartum care.[9,10] From these successful attempts, there was good reason to think that the integration of the psychiatric social worker in the group would be successful although the role was unfamiliar to group physicians.

The absence of alternate workable and patient accessible mental health counseling resources was well recognized by the group's physicians, who in turn expressed interest in and willingness to integrate a county employed psychiatric social worker within the group's practice building. As a contribution to community well-being, the group provided office space at no charge, permitting accessible and convenient patient referral within the clinic.

Economic Deterrents

The continuing growth of insurance covering outpatient non-surgical services and the development of Medicaid, Medicare and other federal-state-municipal programs has increased fiscal access to general health care services for many people. Mental health services, however, have been late inclusions in many insurance policies and are widely excluded in others. The urban distribution of existent public-funded mental health service programs and of private mental health service providers facilitates access to both low income and high income patients in the service area. This characteristic urban distribution of mental health services further adds to their cost of utilization by rural community residents who must travel greater distances for these services than is required for other commonly sought primary care. The 100-mile round trip of a King City resident to mental health resources in the county seat had a definable cost even though the actual service costs were waived or were minimal or not directly experienced (through the payment of a health insuror). With non-availability of public transportation, the estimated private car transportation cost was $12 in 1972. The out-of-pocket costs of unreimbursed private psychiatrist services were $30 to $50 per counseling hour, or a maximum of $30 per hour for county provided psychiatric social worker, psychologist or psychiatrist services.

In southern Monterey County, an area without previous in-community mental health services, the expense and difficulty of arranging transportation and satisfactory babysitter services rendered intensive ongoing counseling efforts virtually unsustainable. The potential for job loss occasioned by missing an entire day's work was increased in the recessional agricultural-based economy. For this rural area, the larger economic deterrents to the referral of a patient for institutional mental health counseling were the direct service costs and, for those eligible for public funded programs, the indirect ones levied by inaccessibility.

Enhancing Economic Accessibility

In devising a mental health counseling strategy for southern Monterey County, an effort was made to extend the "one door" approach whereby all community members irrespective of income level and care funding source are offered access in adjacent clinic and hospital facilities by the same providers. The usual dual system whereby the lowest-income sector unable to pay is referred to a county or municipally operated institution had been ended in the community four years earlier. Five principal funding sources, the state Medicaid program, a local HEW program, the Rural Health Project, Inc., private insurance, personal payment and county funds were available to pay for mental health services.

In this rural area, without private psychiatrists, psychologists, or psychiatric social workers, public employees were utilized to provide services without fee, or on sliding-fee scale, or for Medicaid reimbursement, according to personal means. In the face of frequent non-coverage by medical insurance for mental health services, the sliding scale was of great importance. Thus, scarce personnel could be utilized broadly to serve all community members without the restriction often placed by public institutions on service only to indigents.

Of equal or greater importance was overcoming the out-of-pocket cost of distant accessibility and its impedance to continuity of counseling efforts.

Community Acceptance and Growth of Demand

Community services were initiated late in 1970 with one day a week of service by a psychiatric social worker, with referral strictly from group physicians and project social workers. Within three months, two days of services was required. The growth of referrals from physicians increased vastly with evidence of patient acceptance. Self-referral and referrals from the community's schools and courts began to occur and, in response to a growing need, services were expanded to

three and four days a week. With evidence of current unmet demand manifested by waiting lists of patients and community interest in and support for the program, expansion to seven worker days of service is planned.

Much of the success for acceptance of newly offered mental health counseling has been ascribed to integration of the services in the community's recognized health resource, the community clinic. As a service extended by physician referral on the neutral ground of a multidisciplinary clinic, some of the stigma of referral for mental health was apparently overcome as the patient became one of the 150 to 200 community members daily seeking one or another of health services provided. Other factors for acceptance were the privacy afforded to patients through office location within the clinic and special discretion in medical record management. The excellent rapport which quickly developed between the primary and specialty physicians and social workers was mutually beneficial and this was communicated to patients. Confident referral by physicians to non-physicians for performance of selected health care services previously given only by physicians has been accompanied by strong patient acceptance in two recent studies of patient attitudes toward paramedical personnel.[11,12]

Some unexpected but surmountable factors of community resistance came to light. Rural communities often imagine that they are free of the more frightening and disruptive of behavior problems associated with large cities. Drug abuse, particularly heroin overdosage and hallucinogen intake, had been sporadic local incidents, but unacknowledged community problems. Within a six month period in the emergency room of the community hospital, the author cared for three patients with heroin overdose, three hallucinating patients and three patients made ill by mixed-drug usage. Serving a population of about 22,000, the emergency room is the principal emergency medical facility in a 50-mile radius. The local high school with an enrollment of 1,000 steadfastly refused to acknowledge that there were student drug use problems and that there was need for professional mental health counseling for adolescents. This attitude ended abruptly and the institution became a new referral channel to community mental health resources after the inadvertent drug poisoning of several high school students from prominent local families. The outcome, court-directed mental counseling for some youths and a heightened sense of the need for community mental health resources by community adults, culminated in outspoken support for the programs. The psychiatric social workers organized group counseling for the involved youths within the community.

Unexpected Benefits to the Community

For physicians, social workers and other members of the health care team, the new proximity of mental health professionals led to new input and approaches on patient and problem-family management. Case conferences and consultations by the psychiatric social workers became new avenues within the health care complex for further expanding the demand for and understanding of mental health counseling efforts. Proximity promoted frequent opportunities for discussion of individual patient management.

Within the larger community, psychiatric social workers became frequently invited guests to high school psychology classes and to community groups. Relationships developed, too, with many of the community's ministers, who were pleased to have community referral resources for members of their congregation whose counseling needs exceeded their resources. It is expected that the further growth of in-community mental health manpower will permit expansion of broader mental health education efforts in the community.

Summary

In 1970 the lower Salinas Valley had no in-community mental health services and the principal recognition of need came from physicians who found themselves unable to afford sufficient care to patients with a range of complaints for which they sought physician services. In 1973 the service of two psychiatric social workers, one male and one female, providing four days of service were insufficient to meet existing needs and more time was planned.

Community interest in mental health services of many types is aroused and in the fall of 1973 a youth-centered crisis center with planned counseling service and sheltered home was provided and funded by the four principal valley communities, all under 4,500 population, and several regional social agencies and school systems. The rapidity with which community mental health needs were recognized, service instituted and community funds and manpower mobilized to develop

new community services is impressive in a conservative rural community. The willingness of community members to accept psychiatric social workers suggests a favorable outcome for the development of other non-physician health care professionals in rural communities. The successful integration of these new health professionals within the community clinic further suggests the desirability of the group practice prototype for meeting comprehensive health care needs for the rural community.

ACKNOWLEDGMENT: Douglas Nakashima, MSW, Joseph Gulla, MSW, and Jane Lytle-Vieira, MSW, of the Mon-
Health Services, initiated the experiment here reported, and directed its continuation.
terey County Department of Public Health and Mental

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Teen-Agers and Chronic Medication

ADOLESCENTS HAVE AN ENORMOUS need to be immortal. They feel immortal even if they know they're not. And when they become physically sick or when they're presented with a chronic medication situation, they have to say "no" or want to say "no," because, "if I say yes, I would agree that maybe one day I could die." And this is an intolerable situation, I think, for the adolescent to be in. Adolescents find it inordinately difficult to accept that they will ever die. And this, to some extent, explains why drug propaganda which says anything about a threat to life will not work with adolescents, because, in fact, the young people will prove to you you're wrong. That is if you threaten them with . . . "this drug will do that to you or this drug will do the other to you," they're likely to take it just to show you that it isn't so . . .

—DEREK MILLER, MD, *Ann Arbor*

Extracted from *Audio-Digest Psychiatry*, Vol. 3, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Gassaway AR: Medical Manpower in Oregon (An Informed Commentary). West J Med 121:254-260, Sep 1974

Medical Manpower in Oregon

ALEXANDER R. GASSAWAY, PhD, *Portland*

IN VIEW OF A recently heightened interest in medical geography manifested at the annual Association of American Geographers' meetings, it seems pertinent to review a report on the significance of the local geographic distribution of physician manpower to preventive medicine. The skills of medical geographers (and other researchers with the perception and facility to deal with spatial problems) are sought increasingly to depict and interpret distributions of medical manpower and services for planning under Public Law 89-749 and kindred legislation. Public Law 89-749, the Comprehensive Health Planning Act of 1966, established state and regional comprehensive health planning authorities to cope with the very complex problems of private and public health professions in the endeavor to insure service of high quality to individual and community at reasonable cost and efficiency. Only recently has this law come into full force of implementation in a number of states, including Oregon, the focus of the report titled *Medical Manpower in Oregon** which was published by the Oregon Medical Association (OMA). Researchers studying medical manpower might do well to consider the philosophy and the methods of this research, which attempts to answer the tacitly posed question: "By what means can the adequacy of the areal distribution of physicians be determined in relation to the populations they are supposed to serve?"

The report was published in two parts: The first, presented in 1972, provides regional background data and textual interpretation on the title subject for selected years within the period 1959-72. The first 30 pages are organized into an "Introduction" stating the premises within which the study is molded, six sections of analyses, and conclusions; the latter 95 pages comprise supporting data, in large part originated for this undertaking. The second part, published in 1973 and utilizing information on medical practitioner licensing for that year, extends the background data of the previous portion and provides supplementary detailed statistics on the Portland metropolitan area, the most populous in the state.

This manpower study originated as an "in-house" document for the Board of Trustees of the OMA, under whose aegis it was conducted, in response to the Oregon Comprehensive Health Division's request for a report on personal, comprehensive preventive medical services in the state. The approach to the task employed by the four authors (three doctors of medicine and a medical administrator) was determined by their philosophy stated in the report's "Introduction" (1972, pp. 1-5); essentially:

> It would be highly artificial to separate preventive medicine from curative medicine, as the provision of the former involves . . . the entire medical care delivery system . . . In the broad sense, preventive medicine is synonomous with good patient care. . . The distinction between private and public medicine is not useful in achieving improved medical care in Oregon. Therefore, a study of preventive medicine services necessitates a study of all physicians' services . . . and the prime requisite for preventive medical services is the availability of physicians to a community. . . . [A current crisis in the delivery of health care to individuals is exemplified by] the gaps between the existing and the hoped for medical services . . . which rests clearly on the notion that "health care is a right"; and, therefore, inequities in health services to different

Dr. Gassaway is from the Geography Department of Portland State University.

**Medical Manpower in Oregon* is a book by Harold T. Osterud, Hugh Tilson, Keith Griffin and Robert Dernedde published by the Oregon Medical Association. (Volume 1, 1972; Volume II "Supplement," 1973).

Reprint requests to: A. R. Gassaway, PhD, Department of Geography, Portland State University, P.O. Box 751, Portland, OR 97207.

people in different socioeconomic, racial or geographic categories are no longer tolerable . . . [Health services] should be available, convenient and at reasonable costs. . . . Fundamental to this crisis is the [geographic] maldistribution or absence of manpower, especially in the rural areas and in the socioeconomically deprived areas of the cities.

Consequently, the research quantifies the spatial distributions of primary care and specialist physicians in relation to populations defined by area. It evaluates the adequacies of these distributions for the provision of good health care from six different viewpoints and explores some of the underlying causes of certain maldistributions uncovered in the process. The six viewpoints are, in order of treatment in the report, (a) the traditional patient:physician ratios (for larger regions within the state), (b) a locational quotient—that is, the contrast between extant distributions of office-practice physicians with a hypothetically even distribution according to population, (c) the doctor's office-patient work load, (d) the numbers of practitioners by size of the population centers in which they practice, (e) patient:physician ratios by trade (patient catchment) areas of central places, and (f) defined minimal population thresholds to support different types of practice. Except for approaches (d) by urban center size and (e) by nodal regions, most data are presented for the whole state of Oregon and by each of its 14 official Comprehensive Health Planning (CHP) Areas, individually comprising one or more of Oregon's 36 counties (see Figure 1). The 74 local trade areas were especially derived for the study and they cover the entire state with the exception of a portion of the Portland metropolitan area. In the following discussion these methods will be treated in an order best suited for comparisons.

The study reveals that between 1959 and 1973 the number of licensed physicians in Oregon had increased progressively from 2,110 to 3,177, or at a faster rate (61.2 percent) than the population growth (22.9 percent); and that the population:physician ratio had dropped from an average of 845:1 to 682:1 over the same period, or close to the American Medical Association "optimal" ratio of 650:1. Based on an upward trend of new licensees over the first three years of the 1970's decade, the "optimal" ratio would be reached by 1975.

Such a simplistic approach, however, the report states, masks existing problems of medical manpower availability. State health authorities have expressed considerable concern in recent years over deficient numbers of general practitioners (GP's) and the overall shortage of primary practitioners in general, especially in rural areas. (Primary practitioners include GP's, internists, pediatricians, and a new specialty of "family practitioner" based on resident training, specifically licensed in Oregon first in 1973). Between 1959 and 1972 the numbers of licensed GP's had increased by 1 percent and primary practitioners overall by 19.3 percent, whereas the remaining specialists had increased by 79 percent. Consequently, the population:physician ratios of general practitioners and all primary care doctors had worsened in relation to a state population growth of nearly 23 percent for the period: In 1959 they stood at 1,944:1 and 1,453:1, and in 1972 at 2,482:1 and 1,680:1, respectively. They were decidely improved in the year following (to 2,281:1 and 1,420:1, respectively) as the growth of general practitioners accelerating after 1970 produced net results by 1973. But the average age of GP's was 51 years, and the rate of retirement in the next ten to fifteen years will tend to grow.

Also, the overall population:physician ratios and those of the various specialties vary by CHP and trade areas throughout the state and reflect the disadvantages of most areas outlying the larger centers. The ratios are not only much more favorable in the large centers, but specialists who require higher population thresholds than generalists to support their practices tend to concentrate overwhelmingly in the metropolitan areas, especially in Portland, the largest. (According to the 1970 census, the urbanized portions of Oregon's three metropolitan areas had the following populations: Portland, the Oregon portion, 752,000; Eugene, 139,000; and Salem, 93,000. The cities of Corvallis and Medford, the state's fourth and fifth largest, had populations of 35,000 and 28,000, respectively. All lie in the heavily populated Willamette Valley of western Oregon, except Medford, which is situated considerably farther south in a mountain valley near the California border. (See Figure 1.)

Two other measures that were applied lend support to these generalizations. According to the locational quotient, in 1970 CHP Area 2 which contains the Portland metropolitan area should have had 21 percent (280) fewer physicians, and

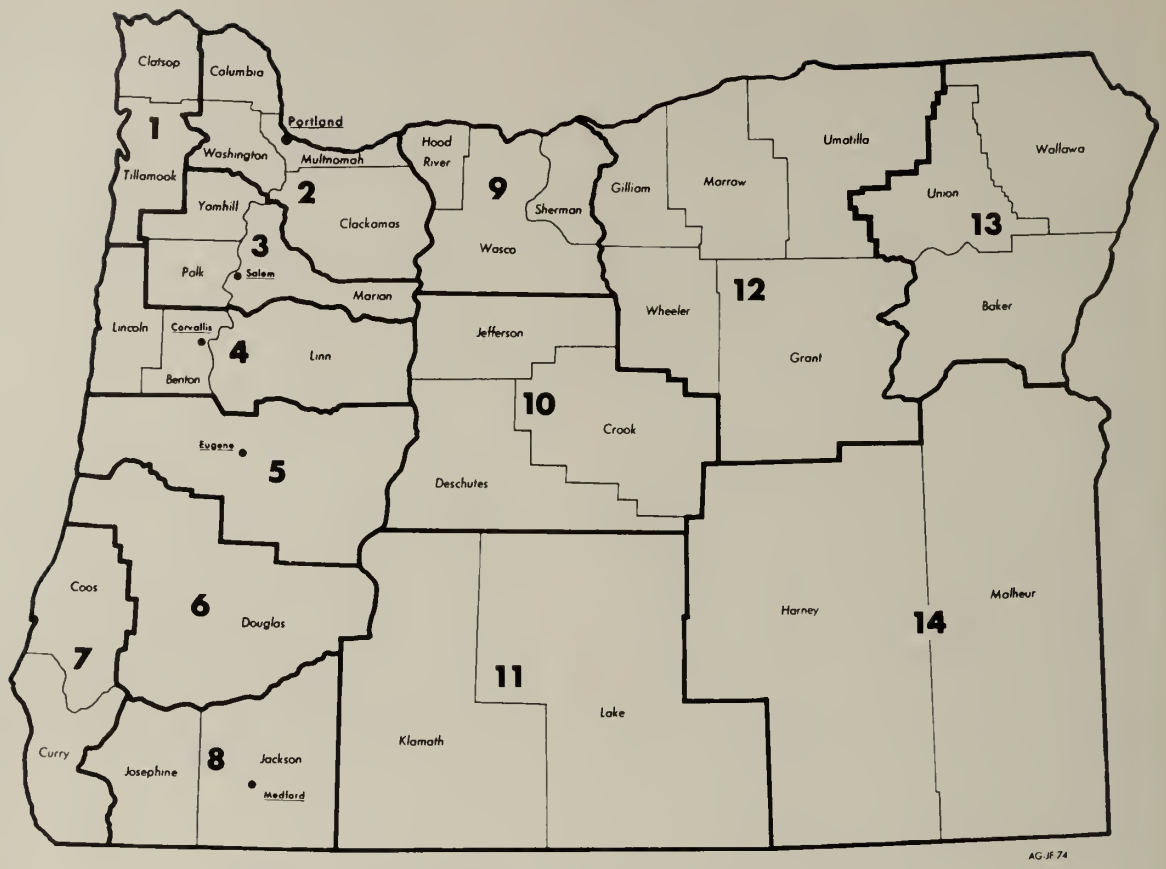

Figure 1.—Comprehensive health planning regions in Oregon.

all other regions should have had between 5 percent and 65 percent more than in actuality. Those regions containing the cities of Salem, Corvallis and Eugene (Areas 3, 4, and 5) fared more favorably by this approach than most outside the Portland area.

The second measure treats the distribution of types of physicians by the size of the urban place in which they practiced during selected years within the study period. (The urban places are not specified, but are grouped into seven categories of population size ranging from centers of "less than 5,000"— referred to in the report as "rural areas"—to "over 300,000.") According to these data, of the 715 new physicians in Oregon between 1959 and 1970, over two-thirds took up practice in the state's metropolitan areas where 65 percent of the population was located in the latter year. By contrast, only 2 percent sought practice in "rural areas" where an agglomerated 4.9 percent of the population was situated. (This low figure of 4.9 percent derived by the reviewer, gives no indication of the probably fair portion of the additional 26 percent, non-agglomerated rural population which must be served by these same physicians.) Furthermore, the rural areas, which depend largely upon generalists, lost 44 general practitioners (or 18 percent of the 1959 total) over the 11-year span, and this loss was not compensated for by the gain of only five other primary practitioners. The upturn in physician registrations in the state post-1970 brought only nine additional primary practitioners to rural settlements by 1973.

The traditional measure of physician manpower adequacy (the population:physician ratio) does not indicate the actual patient load carried in office practice, for among other things not all people in a population utilize doctors' services equally and not all physicians choose to carry the same work load. Therefore, an Office-Practice Survey covering the year 1970 was implemented to gain better knowledge of physicians' actual patient loads and to determine certain attitudes about practice. The data in the report derived from the 51 percent response to survey questionnaires mailed to 2,175 physicians in active office practice in Oregon. ("Office practice" physicians excluded

those in the support services of pathology, anesthesiology, radiology, administration, public health, and the like). Most data indicate the average work load for each type of practice in each CHP Area by the number of different patients per physician, yearly and weekly numbers of office visits per physician, and by numbers of office visits per patient per year.

The survey indicated that the mean number of patients' office visits per year was 5,556 to all types of physicians for the state. It was lowest (4,926) in the "Portland region," Area 2, with the largest numbers of doctors of any region, but highest in the sparsely physicianed plateau-and-mountain northeastern portion of the state (Areas 12 and 13 with, respectively, 7,751 and 7,919 visits per physician). The Portland region averaged fewest individual patients per physician (746) but the largest number of office visits per patient (6.6). This contrasts with Area 12's 1,722 individual patients per practitioner, and 4.5 visits from each. (One can assume the Portland situation is attributable to the larger number of specialists there spending more time with fewer patients, and the greater access to medical care for a portion of the population through the main Oregon facilities of the Kaiser prepaid medical plan.) Furthermore, the study finds that the general practitioners, who represented only 31 percent of the state's physician manpower, received over half (52.3 percent) of the total visits—primary practitioners collectively, three-quarters, with the remaining visits to specialists. The heaviest average patient load for both primary physicians and specialists was in the northeastern portion of the state (where most practitioners are in primary practice), ranging above the average for the state by 25 percent and 67 percent, respectively.

The survey reflects physician maldistribution in the sense that where there are fewer practitioners, patient loads exceed the average and, assuming the seriousness of illness of patients distributes evenly among physicians, these doctors are relatively overworked and give their individual patients relatively less service.

There are difficulties in attempting to determine areal deficiencies by regions the size of CHP Areas. An obvious problem is the locational origin of particular physicians' patients owing, for example, to the proximity of smaller-place and farm populations to larger towns and cities among which there is choice of service. (Ideally, the reviewer notes, patient-origin studies are relied upon to determine patient source—time-consuming and costly endeavors. The last such study in Oregon was in 1967 by the Oregon Regional Medical Program and partially covered the origin of hospital patients only. A more complete hospital patient-origin study currently in progress by the same organization should be ready soon. In time, the records from peer reviews of patient treatments currently being set up in Oregon by OMA in accordance with federal legislation are expected to provide patient-source information for about 80 percent of office patients also.)

Consequently, in the absence of recent or complete data from patient-origin studies at the time the research was undertaken, the authors derived the trade areas of individual central places (or of several centers collectively, where evidence warranted), having at least primary medical care. For each nodal area, data were compiled to show ratios of population to (1) all active physicians and (2) primary care physicians. The regions were delimited, an interview with author Dernedde reveals, from 1970 census population tract maps and data, Oregon Board of Medical Examiners licensee lists, and highway maps; and each region included that population closer to a particular central place (or places) with physician care than to others. All regions were checked by telephone interviews with local physicians and from other sources and were modified where this information indicated other than the originally assumed patient movements.

This approach rested on several assumptions (1972, pp. 19-20): (1) Comprehensive health care, because of its non-crisis nature, must be convenient and readily accessible with minimum loss of time. (2) The primary care physician, along with paramedical personnel, will deliver this type of service. (Smaller places almost invariably have a general practitioner before a specialist.) (3) Most people prefer to have their primary care close to home and will get it, if possible, in the central place where they shop or receive most of their services. But the authors add, "Undoubtedly many people living not only close to the cities, but from whatever distance, will go to the metropolitan area for specialty care" (which would appear to reduce the accuracy of the ratio of patients to all active physicians). (If the bases for these assumptions are not fairly obvious, they are supported in Ciocco A, Altman I: "Medical Service Areas and

Distances Travelled for Physician Care in Western Pennsylvania," Public Health Monograph No. 19. U.S. Public Health Service, HEW 1954.)

Eleven places are guardedly suggested (1972, p. 20) as having "physician shortage" based on a ratio of more than 2,000 persons per primary physician, even if the central place falls into a trade area near other medical care—a definition of "shortage" the authors believe the reader willing to accept. Surprisingly, the list includes five centers—not the entire trade areas—in the four counties making up the "Portland region," as against only four in northeastern Oregon's Area 12; and, according to the 1970 census, they comprised a total population of between 65 and 70 thousand, depending upon the interpretation of the area reference. By the yardstick of one primary care doctor for every thousand persons, the report notes, only four places in the state (excluding Portland) would have adequate primary physician care.

From the information obtained by the methods discussed so far, the authors express belief that Oregon in the aggregate appears successful in gaining overall numbers of physicians, especially among the specialists; but that the state is not overcoming several very real problems—"notably problems of progressive shortages of primary care specialists and general practitioners and . . . weakening of the non-urban medical care network" (1972, p. 23). Thus, they desired to assess "the absolute severity of the problem" by a recognized standard for projecting the "need" for physicians, by specialty by area, from data on existing distribution patterns. Though long argued by medical manpower experts, no "ideal" method has ever been devised for this purpose:

> Projections based on morbidity statistics break down because of inaccuracies of our epidemiological reporting system [not to mention non-communicable disease reporting] and our inability to agree on uniform medical delivery standards. . . . Econometric demand projections require information about our population which is not available and make assumptions about the sameness . . . of need which are unacceptable to many physicians. (1972, p. 23)

Therefore, methods similar to those employed by the U.S. Department of Health, Education and Welfare and the President's Health Manpower Commission were adopted. The numbers of physicians required regionally were determined by the application of "ideal" ratios of population-per-physician for 16 types of practices to the 1970, 1972, and 1973 populations of each CHP Area and of Oregon as a whole. The "ideal" ratios were obtained from *Medical Economics* (30 Oct. 1967, pp. 67-70) and represent minimum thresholds of population to support different types of practices—for example, 1:2,000 for general practitioners, 1:5,000 for internists, 1:10,000 for pediatricians, general surgeons and psychiatrists, 1:100,000 for neurosurgeons. The results were compared with numbers of physicians in active practice in those areas, and "surpluses" or "shortages" were compiled to give an indication of manpower supply trends. The same ratios were reapplied to populations extrapolated by linear trend to 1981 to estimate the need for that year. No attempt was made to predict actual physician supply to meet those needs.

The results indicated that the 964 active GP's in Oregon in 1973 were 138 short of the desired 1,092. The projected need for 1,226 GP's in 1981 may be difficult to obtain in view of the anticipated higher rate of retirement over the next decade or so. The considerable, but less severe, shortages of internists and pediatricians brought the overall deficit of primary practitioners to more than 300 in 1973. By contrast, according to the system of estimation employed, ophthalmologists, urologists, neurosurgeons, dermatologists and orthopedic surgeons were in excess for the state as a whole, the latter by 100 percent. All other specialists were in greater or lesser degree of deficit in spite of substantial increases in numbers of certain types after 1970. A great dearth of psychiatrists persists in spite of the fastest growth of this type of practitioner among all specialists in recent years in the state.

A careful examination of the report's tabular data indicates considerable contrast between the surplus-and-deficit situation for the region containing the primate city and most of the remainder of Oregon. For example, the Portland region in 1973 had 83 of Oregon's 138 total shortage of GP's; it had a surplus of 88 internists in contrast to the state shortage of 17; and it had an excess of 13 pediatricians as against the state's deficit of 56. It is difficult to assess Portland's surpluses, however, as this metropolis draws referrals from far and wide. There is also the question of the degree to which some specialists engage in general practice. Other sizable deficits exist in the Eugene and Salem metropolitan regions of the Willamette

Valley and in Area 6 (Douglas County), the hilly region just south of the valley.

In approaching the basic question of the adequacy of the geographic distribution of physicians in Oregon, the authors have recognized the limitations of any one method individually and have made their assessment from the composite picture of several methods employed simultaneously. What comparability of result exists among these methods—for example, those four which employ the same basic region, the CHP Area? (Reference to (a) actual population:physician ratios, (b) locational quotients, (c) the physicians average annual work load and (f) the ideal population thresholds to support certain types of practices.) To examine comparability, the reviewer first compiled percentages of surplus/deficiency for the second and fourth approaches and then ranked each CHP Area from "most to least adverse" as to its value under each of the four methods. The most recent information within the report was used in each case, and the three highest- and three lowest-ranking positions were tallied. Due consideration was given to sufficient interval between ranked positions. One must remember that the results of approaches (a) and (c) represented actuality, whereas those of (b) and (f) represented how greatly actuality differed from an ideal. There are admittedly problems with such an approach, but the results were revealing of the overall picture.

All methods indicated that the Portland region (Area 2) ranked overall most favorably for both specialists and primary care, though short of GP's. By contrast, the areas appearing in the most adverse situations by all measures (considering the *percentage* values of the locational quotients and ideal ratios) were the more sparsely populated Areas 12 and 13 in northeastern Oregon and Area 11 in the relatively dry south-central part of the state. The *absolute* values of the quotients and ideal ratios, however, rank the Willamette Valley Areas 3, 4 and 5 especially deficient—the conflict between relative and absolute values. In Oregon's areas of greater relative deficiency, the proportionally greater deprivation of a numerically few lacking physicians in the lesser populated portions of the state may be more difficult to offset, owing to the paucity of social amenities offered, than the far greater absolute deficiency in areas offering more cultural advantages.

The ranking approach breaks down, however, for the ideal thresholds in counties having small populations, especially in eastern Oregon, in relation to the high ratios applied so that the total deficiency for a number of CHP Areas and a variety of specialties is just one physician each. (Ten Oregon counties had population less than 10,000 in 1970, and six had less than 5,000.)

Further differences gleaned by the reviewer from the results of the measures employed are significant—for example, the enigma of Area 6, Douglas County. Here the locational quotient indicated a need in 1970 for 53 percent more physicians in keeping with its population, and the office practice survey revealed the highest number of actual patients per physician in Oregon—47 percent above the state average (1972, pp. 62, 64). Yet the mean number of patient office visits to primary practitioners is only 3 percent above the state average, only 12 percent above the state average for all practitioners, and the average number of visits to pediatricians is the lowest among the CHP Areas having this type of service. Assuming the incidence of morbidity to be no less than elsewhere in the state, these apparent anomolies would suggest further research as to the level of family incomes and the proportion of them spent on medical care in Area 6, and in other areas having circumstances similar to those cited.

A sharply contrasting situation exists south of Douglas County in Area 8 in the mountains just north of the California border. This region, having none of the census metropolitan areas but with the small city of Medford as its main center, ranks second to Portland in overall physician services. Graced with moneyed timber interests and proximity to Pacific coastal and highland outdoor recreational facilities, it is reputed in Oregon as an ideal place for family living. A 34 percent population growth from 1960 to 1973 would support this premise. This and a host of other evidence would suggest the contentions of such as Pierre de Vise* and J. W. Hambleton† that noneconomic criteria including amenity location are often more important in physicians' location than income or patient need.

Several other comments on the content and philosophy of the OMA publication seem appropriate. The authors note with reference to areas that have visible physician deficits and have lim-

*Misused and Misplaced Hospitals and Doctors, A Locational Analysis of the Locational Health Care Crisis. Washington; Assoc. of American Geographers, 1973, pp 44, 69-72.

†Determinants of Geographic Differences in the Supply of Physicians' Services, (Ph.D. Dissertation). Department of Economics University of Wisconsin, 1971, p 33.

ited access to areas more favorably supplied: "This begs the question of access—*i.e.*, how far away before there are barriers which . . . diminish . . . the physician's opportunity to practice preventive medicine? This question will be investigated in depth in the discussion section of this report" (1972, p. 20). One might apply the question to aspects of curative medicine as well, and comment that the fact that the question of "how far" is never treated is a disappointment to the geographer. Whereas this study emphasized Oregon outside the Portland area, a future study might profitably consider this question within the metropolis. The residents of the Albina ghetto, Portland's Model Cities area, for example, have had difficulties making the seven-mile journey to the out-patient clinics of the county hospital by bus with several transfers involved.

Geographers may challenge the latter portion of the statement: "The trade area approach overcomes some of the weaknesses inherent in the population-specific data [*i.e.*, on population:physician ratios and the number of physicians by size of urban place], but also has inherent in it the drawback of being particularistic and precluding generalization," (1972, p. 20). This is a misconception by the authors, for geographers by and large utilize the regional approach as a framework in the process of generalization. Most certainly the authors are aware that it is a lack of patient-origin data on the longer-distance movement of patients to specialist care—the need for *more representative* regionalization—that is the primary drawback to generalization in this case. Local researchers can expect the deficient data for hospital patients to be offset by the Regional Medical Program patient-origin study (above) and, it is hoped that the Physician Index Subcommittee of the Portland Metropolitan Area Comprehensive Health Planning Association will be funded to gain information on office-patient origin.

What clues have we as to why rural areas in Oregon continued to lose physicians, general practitioners for the most part, who in turn were not being replaced by new licentiates? There are two sources of information (1972, pp. 21-23). The first was a questionnaire to the 56 members of the 1970-71 senior class of the University of Oregon Medical School as to their choice, *inter alia,* of community of practice by population size. Less than 3 percent desired practice in centers of under five thousand and only 13 percent sought centers of five to ten thousand. (The largest portion, nearly 40 percent, chose communities of ten to fifty thousand, about 20 percent chose cities the size of Eugene and Salem, another 20 percent the Portland metropolitan area, and a small remainder was undecided.) Their preference for other than rural areas may be explained partially by answers to a question put to practicing physicians in the Office Practice Survey conducted by the OMA in 1970 (above): Would the doctor practice in an area of less than five thousand and, if not, why not?

> The overwhelming reason that psychiatrists, surgeons and obstetricians would not practice in a rural area was because there were not enough patients to support their [particular] practice . . . [The reasons for GP's appear representative of all primary practitioners in that] problems of financing, lack of culture, or extracurricular activities and educational opportunities for families, the inadequate facilities available as well as overwork are the major reasons for their not wanting to settle in . . . rural areas (1972, pp. 22-23).

Some measure of relief to this problem has materialized very recently, however, from a dramatic rise in the number of newly licensed physicians. Records of the Oregon Board of Medical Examiners indicate 82 new physicians were licensed in 1971, contrasted with 185 in 1972 and about 600 in 1973. This coincides with the progressive removal in Oregon of stipulations of a basic science examination (which had existed in addition to other requirements). That requirement was terminated in April, 1973, for out-of-state applicants, following the earlier examples of Washington, New Mexico and Arizona, among others. And among the increased numbers of newly licensed general practitioners, more are seeking practice in the smaller communities.

Overall, *Medical Manpower in Oregon* is an eminently worthwhile, practical and timely study elucidating the adequacy—and the inherent problems in determining that adequacy—of the geographic distribution of physicians in view of the coming demands of national comprehensive health care.

Chinese Herbal Medicines

CHINESE "HERBAL REMEDIES" containing substantial quantities of undeclared phenylbutazone and aminopyrine have been associated with the recent death of one person and the hospitalization of four others due to agranulocytosis. All five persons were caucasians, four from the San Francisco area and one from Minneapolis.

Analysis disclosed that the pills they had used contained up to 30 mg phenylbutazone per pill and 30 mg aminopyrine per pill. Typically the label directions call for taking 12 to 18 pills a day. The labels on the packages list only the herbal ingredients.

The herbal remedies encountered to date are hard, spherical black or brown tablets approximately ¼-inch in diameter. The drug containers are occasionally packed in bright-colored cardboard boxes with pictures depicting men and woment suffering from back or leg pains.

Several brand names and firms are involved to date. Typical labeling for such products includes the following indications: arthritis, rheumatism, headache, anemophobia, paralysis, back neuralgia, bone pain, acute or chronic neuralgial and other pain caused by rheumatism. Some products are offered for promotion of the circulation of the blood or for sexual rejuvenation.

These drugs reach the United States illegally, apparently by individual mail shipments or in personal luggage. They are distributed within the United States largely through non-commercial channels, but have been found available in specialty stores (such as Chinese grocery stores and gift shops).

These irregular modes of entry and distribution mean that the usual regulatory procedures of the FDA and the U.S. Customs Service can not be fully successful in preventing availability of these products. Therefore, through publicity and individual visits, State and Federal authorities have attempted to inform the people most likely to use these drug products about the hazards involved, and have visited likely commercial outlets.

Although phenylbutazone and aminopyrine have led to the toxic reactions detected so far, other undeclared potent drugs also may be present in these herbal remedies. Additional drugs reported to date are methyltestosterone, prednisolone, diazepam, chlorozoxozone (a "skeletal muscle relaxant"), and acetaminophen, in amounts such that the recommended 12 to 18 pills a day would provide approximately therapeutic doses.

Any physician encountering a patient with agranulocytosis should consider the possibility that the patient has been using a Chinese herbal remedy containing phenylbutazone or aminopyrine or both. In addition, the Food and Drug Administration recommends that physicians and other health professionals advise any persons using such products to discontinue their use.

Any information concerning adverse reactions to Chinese herbal remedies as well as information related to their sale and distribution may be transmitted to FDA by contacting the nearest FDA office.

LIST OF PRODUCTS AND COMPANIES

Long Life Brand Ginseng Hui Sheng Tsaitsaowan	Nan Lien Pharmaceutical Co. Ltd.
Chui Fong Toukuwan Nan Lien	Nan Lien Pharmaceutical Co. Ltd.
Sanlung Pai Ginseng Hui Sheng Tsai Tsao Wan	Nan Lien Pharmaceutical Co. Ltd.
Fonsuning Tongwan Lilong Pai	Nan Lien Pharmaceutical Co. Ltd.
Hippo Brand Secret Formula Chui Fung Eng	Nan Lien Pharmaceutical Co. Ltd.
Chihshihton	Ichongtai Pharmaceutical Co. Ltd.
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Shou Sing Chui Fong Toukuwan	Shou Sing Pharmaceutical Co. Ltd.

From FDA Drug Bulletin, July 1974.

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1:30 p.m.	Meeting of the House of Delegates

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6:30 a.m.	Registration
7:15 a.m.	Call to Order, Welcome Address
7:30 a.m.-noon	Scientific Sessions
8:00-10:00 p.m.	Fireside Chats—Sponsored by the Hawaii Thoracic Society. (Informal discussion of selected topics.)

WEDNESDAY, OCTOBER 30, 1974

7:00 a.m.	Registration
7:30 a.m.-noon	Scientific Sessions
1:00 p.m.	Meeting of the House of Delegates

THURSDAY, OCTOBER 31, 1974

7:00 a.m.	Registration
7:30 a.m.-noon	Scientific Sessions
12:00 noon	Luncheon—Imperial Room Address by Malcolm C. Todd, M.D., F.A.C.S., President, American Medical Association Inauguration of New Officers and Presentation of Awards

FRIDAY, NOVEMBER 1, 1974

7:30 a.m.-noon	Scientific Sessions
6:00 p.m.	Sportsmen's Night Dinner Presentation of Awards

SPECIAL GUEST SPEAKER

MALCOLM C. TODD, M.D., F.A.C.S.
President, American Medical Association

SELECTED GUEST FACULTY

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Texas Tech University School of Medicine, Lubbock

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Post Oak Psychiatry Associates, Houston

ALLEN J. ENELOW, M.D.
Chairman, Department of Psychological and Social Medicin
Presbyterian Hospital, Pacific Medical Center, San Francisc

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Professor of Medicine, Head, Department of Developmental Therapeutics
The University of Texas Cancer Center, Houston

DEAN T. MASON, M.D.
Professor of Medicine, Professor of Physiology
Chief, Cardiovascular Medicine
University of California, Davis

KENNETH L. MELMON, M.D.
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School of Medicine, University of California, San Francisco.

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Co-Director, Clinical Pharmacology Unit
College of Medicine, University of Vermont, Burlington

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Vice-President and Medical Director
Mead Johnson Research Center, Evansville, Indiana

IRWIN ZIMENT, M.D.
Assistant Professor of Medicine, UCLA School of Medicine
Director, Respiratory Therapy, Harbor General Hospital
Torrance

For additional information regarding the program or travel arrangements, write:

HAWAII MEDICAL ASSOCIATION
University of Hawaii, Conference Center, CCECS
2500 Dole Street, Honolulu, Hawaii 96822

in memoriam

BANDELIER, ROYALL H., Los Angeles. Died April 26, 1974 in Los Angeles of kidney failure after aneurysm operation, aged 83. Graduate of Indiana University School of Medicine, Indianapolis, 1916. Licensed in California in 1926. Dr. Bandelier was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

BARNARD, HAROLD D., Palm Desert. Died January 17, 1974 in Palm Desert, aged 78. Graduate of the University of Michigan Medical School, Ann Arbor, 1919. Licensed in California in 1922. Dr. Barnard was a member of the Riverside County Medical Association.

BARTOK, THOMAS, Los Angeles. Died June 11, 1974 in Los Angeles of injuries received in an automobile accident, aged 52. Graduate of Lorand Eötvös University of Budapest, 1951. Licensed in California in 1960. Dr. Bartok was a member of the Los Angeles County Medical Association.

BINGHAM, ELMER MCKINLEY, Pioneer. Died July 25, 1974 in Jackson, California, aged 72. Graduate of the University of Wisconsin Medical School, Madison, 1929. Licensed in California in 1930. Dr. Bingham was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

CHAN, RAYMOND, Concord. Died July 5, 1974 in Concord of cardiac standstill - uremia, aged 56. Graduate of the University of Louisville School of Medicine, 1949. Licensed in California in 1950. Dr. Chan was a member of the Alameda-Contra Costa Medical Association.

CUTLER, CHARLES HENRY, Carmichael. Died February 7, 1974 of pulmonary insufficiency due to emphysema, aged 64. Graduate of the University of Southern California School of Medicine, Los Angeles, 1938. Licensed in California in 1941. Dr. Cutler was a retired member of the Sacramento County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

DICKEY, LLOYD B., San Rafael. Died July 18, 1974 in San Rafael, aged 80. Graduate of the University of Minnesota Medical School, Minneapolis, 1923. Licensed in California in 1924. Dr. Dickey was a member of the San Francisco Medical Society.

DYKES, JACK, Bakersfield. Died July 30, 1974 in Bakersfield of heart disease, aged 53. Graduate of Northwestern Medical School, Chicago, 1944. Licensed in California in 1945. Dr. Dykes was a member of the Kern County Medical Society.

FOULKS, CHARLES ALLISON, JR., Long Beach. Died July 13, 1974 in San Diego of brain stem infarction, aged 71. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1930. Licensed in California in 1931. Dr. Foulks was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

GOLDYNE, ALFRED JOSEPH, San Francisco. Died July 18, 1974 in San Francisco of complications following surgical operation, aged 62. Graduate of the University of Illinois College of Medicine, Chicago, 1937. Licensed in California in 1943. Dr. Goldyne was a member of the San Francisco Medical Society.

GROVE, HOWARD R., Bakersfield. Died July 20, 1974 in Bakersfield of cancer, aged 61. Graduate of State University of Iowa College of Medicine, Iowa City, 1938. Licensed in California in 1939. Dr. Grove was a member of the Kern County Medical Society.

KIRTLAND, HOWARD B., JR., San Diego. Died July 10, 1974 of heart disease in San Diego, aged 56. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1944. Licensed in California in 1944. Dr. Kirtland was a member of the San Diego County Medical Society.

KOHL, ROY DOUGLASS, Los Angeles. Died July 20, 1974 of heart disease, aged 75. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1925. Licensed in California in 1925. M.D. degree from California College of Medicine, 1962. Dr. Kohl was a member of the Los Angeles County Medical Association.

LARUS, NORMAN JACKSON, Palm Springs. Died June 5, 1974 in Palm Springs, aged 54. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1945. M.D. degree from California College of Medicine, 1962. Dr. Larus was a member of the Los Angeles County Medical Association.

MARTIN, IVAN ELWOOD, Modesto. Died June 17, 1974 in Washington, DC, aged 59. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1941. Licensed in California in 1941. Dr. Martin was a member of the Stanislaus County Medical Society.

MOON, HENRY D., San Francisco. Died August 2, 1974 in San Francisco, aged 59. Graduate of the University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Dr. Moon was a member of the San Francisco Medical Society.

MOSHER, WALTER FREDERICK, Ventura. Died July 5, 1974 in Ventura, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1914. Licensed in California in 1915. Dr. Mosher was a re-

tired member of the Ventura County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Oliva, George, jr., San Anselmo. Died July 14, 1974 in San Anselmo, aged 64. Graduate of the Creighton University School of Medicine, Omaha, 1934. Licensed in California in 1937. Dr. Oliva was a member of the Marin Medical Society.

Rampoldi, Henry Darr, Martinez. Died July 29, 1974 in Martinez of acute leukemia, aged 68. Graduate of McGill University Faculty of Medicine, Montreal, 1940. Licensed in California in 1940. Dr. Rampoldi was a member of the Alameda-Contra Costa Medical Association.

Ratner, Reuben, Beverly Hills. Died July 4, 1974 in Yugoslavia of heart disease, aged 76. Graduate of Rush Medical College, Chicago, 1928. Licensed in California in 1928. Dr. Ratner was a member of the Los Angeles County Medical Association.

Reardan, Frank B., Sacramento. Died July 22, 1974 in Sacramento, aged 84. Graduate of Cooper Medical College, San Francisco, 1911. Licensed in California in 1911. Dr. Reardan was a member of the Sacramento Medical Association.

Roberts, James Eugene, Stockton. Died February 12, 1974 of cerebrovascular accident, aged 55. Graduate of the University of Southern California School of Medicine, Los Angeles, 1944. Licensed in California in 1944. Dr. Roberts was a member of the San Joaquin County Medical Society.

Searls, Henry Hunt, San Francisco. Died June 22, 1974 in San Francisco of heart disease, aged 82. Graduate of the University of California Medical School, Berkeley-San Francisco, 1916. Licensed in California in 1916. Dr. Searls was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Sutton, Charles Edward, Los Angeles. Died July 4, 1974 in Sepulveda of heart disease, aged 60. Graduate of St. Louis University School of Medicine, 1937. Licensed in California in 1957. Dr. Sutton was an associate member of the Los Angeles County Medical Association.

Williams, Anson P., Glendale. Died July 5, 1974 in Glendale, aged 62. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1936. Licensed in California in 1936. M.D. degree from California College of Medicine, 1962. Dr. Williams was a member of the Forty-First Medical Society.

Williams, Wilburn J., Los Angeles. Died July 3, 1974 in Los Angeles, aged 70. Graduate of the University of Illinois College of Medicine, Chicago, 1928. Licensed in California in 1938. Dr. Williams was a member of the Los Angeles County Medical Association.

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INJECTION

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(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. polyvinylpyrrolidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS

INJECTION

Bicillin® LONG-ACTING

(STERILE BENZATHINE PENICILLIN G SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

(Continued from Page 24)

PHYSICIANS WANTED

PHYSICIAN to work in community clinic in Southern California town of about 60,000. Spanish-English desirable. $22,000 to $26,000. Contact Escondido Community Clinic, 401 N. Spruce, Escondido, CA 92025, (714) 747-6610.

SOUTH LAKE TAHOE-EL DORADO COUNTY—Internist and Pediatrician needed. Presently only one internist and no pediatricians. New office available across from the hospital. South Lake Tahoe is a year-round recreation area. Call (916) 541-2994.

FAMILY PRACTICE FACULTY—Innovative, University-affiliated, urban-centered Family Practice Residency at San Francisco General Hospital needs board-eligible/qualified Family Physician with practice experience to join faculty. Duties will include: Teaching and consultation in Model Family Practice Unit (40 percent); direct patient care (20 percent); program development (40 percent). Respond with curriculum vitae to: Robert J. Massad, MD, Director, Family Practice Residency Program, San Francisco General Hospital, No. 1001 Potrero, Building 9 - Room 326, San Francisco, CA 94110.

SITUATIONS WANTED

NEUROLOGIST seeks relocation in California. Extensive experience and competent in clinical neurology as well as Neuro-radiological procedures, EEG and EMG. Please reply by airmail. Box 9397, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, 39, AP - CP certified, seeks position as Associate or Director, experienced. Write Box 9380, Western Journal of Medicine, 731 Market Street, San Francisco 94103.

PRACTICES FOR SALE

SURGEON-GP, leaving to join medical group in December, 1974, has well-equipped, 1,500 square ft. office available. As well as 10-year-old well-established practice in great location in Huntington Beach. Excellent terms available. Write Box 9398, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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Join an expanding HMO on the island of Guam, gateway to Micronesia and the Orient. Opportunity for travel—one week's vacation every two months plus other outstanding benefits. Career opportunity to return to our mainland facilities. Selected openings in:

Family Practice — Pediatrics
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Orthopedics

Also, opening for a Medical Director—Guam facility. Will practice medicine and devote up to 25 percent in administrative duties. Specialty in one of above. Contact: Frank Volpe, MD, Medical Director, Family Health Program, Room 9419, 2925 N. Palo Verde Ave., Long Beach, CA 90815.

POSITIONS WANTED

ADMINISTRATIVE OR MEDICAL DIRECTOR situation desired by 48-year-old certified surgeon. Licensed in California. Can furnish both personal and professional references. Reply Box 9393, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ASSOCIATES WANTED

WANTED: ASSOCIATE FOR ALLERGY AND CLINICAL IMMUNOLOGY PRACTICE in North San Diego County. No investment necessary. Excellent opportunity for a young individual interested in growth. Box 9395, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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RESECTOSCOPES—BOVIE—2-27 Thompson—Extras—$90 Each. BB-2 Sheaths—$225. Liebel F. Bovie—$275. R. Hamm, MD, 1580 No. Laurel, Upland, CA 91786.

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SOUTHERN CALIFORNIA, VALENCIA/NEWHALL—Rapidly growing area near San Fernando Valley. 24,000 square ft. medical building now under construction, completion early Fall 1974. 50 percent leased; less than 3 minutes from 2 hospitals. Only deluxe facility in area, ample convenient parking. Suites built to your specifications. For information call (714) 640-0760 or write to JPH Enterprises, 240 Newport Center Dr., Newport Beach, CA 92660.

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FULLY AND HANDSOMELY FURNISHED OFFICE in San Diego's beautiful Mission Bay area. (45¢ per sq. ft.) Family practice equipment rental included. X-ray optional. Established practice location in small medical building. 900-1,300 sq. ft. available. R. C. Mowry, MD, 1300 Grand Ave., San Diego, CA 92109; (714) 273-4285.

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ASK ABOUT OUR WEEKLY MARKET REPORT

When a cough spoils your patient's day...

riaminic® Expectorant

Each teaspoonful (5 ml.) contains:
ninic, 25 mg. (phenylpropanolamine hydrochloride, 12.5 mg.; eniramine maleate, 6.25 mg.; pyrilamine maleate, 6.25 mg.); glyceryl guaiacolate, 100 mg.; alcohol, 5%.

Triaminic® Expectorant with Codeine ©

Each teaspoonful (5 ml.) contains:
Codeine phosphate, 10 mg. (Warning: May be habit forming); Triaminic, 25 mg. (phenylpropanolamine hydrochloride, 12.5 mg.; pheniramine maleate, 6.25 mg.; pyrilamine maleate, 6.25 mg.); glyceryl guaiacolate, 100 mg.; alcohol, 5%.
Triaminic Expectorant with Codeine is a Schedule V controlled substance.

The Adult Expectorants that are great for kids, too.

Dorsey Laboratories/Division of Sandoz-Wander, Inc./Lincoln, Nebraska 68501

B--RB

The Role of the Detail Man

Opinion & Dialogue

Dr. Willard Gobbell
Family Physician
Encino, California

"I may be prejudiced, but I a very much in favor of the detail m I meet. Most of them are knowled able about the drugs they promote and can be a great help in acquair ing me with new medication."

Family Physician's Perception

I think that most general practitioners in this area feel as I do about the detail man. Over the years I have gotten to know most c the men who visit me regularly an they in turn have become aware o my particular interests and the na ture of my practice. They, therefore, limit their discussion as muc as possible to the areas of interes to me. Since I usually see the sam representative again in future visits, it is in his best interest to supply me with the most honest, factual, as well as up-to-date information about his products.

Dr. Jeremiah Stamler
Chairman
Department of Community Health and Preventive Medicine, and Dingman Professor of Cardiology
Northwestern University Medical School

"In the total picture of deali with health problems in this cour there is a potential for detail men to play a meaningful role."

The Positive Influence

My contact with representatives and salesmen of the pharmaceutical industry is the type of co tact that people in a medical cent research people, and academic people have and that's in all likeli on a somewhat different level fro that of the practicing physician.

Let me touch on how I perso ally perceive the role of the sales representative. These men reach large numbers of health professionals. Thus they could be—anc at times actually are—dissemina tors of useful information. They could consistently serve a real ec cational function in their ability t discuss their products.

At present they do distribut printed material, brochures and pamphlets—some of it scientific ally sound and therefore truly us ful—as well as some excellent fil produced by the pharmaceutica industry. When they function in

e a Source of Information?

Yes, with certain reservations. average sales representative a great fund of information it the drug products he is re- sible for. He is usually able to ver most questions fully and ligently. He can also supply nts of articles that contain a t deal of information. Here, exercise some caution. I usu- ccept most of the statements opinions that I find in the rs and studies which come the larger teaching facilities. s without saying that a physi- should also rely on other ces for his information on macology.

ing of Sales Representatives

Ideally, a candidate for the ion as a sales representative harmaceutical company d be a graduate pharmacist has a questioning mind. I don't this is possible in every case, o it becomes the responsibility of the pharmaceutical company to train these individuals comprehensively. It is of very great importance that the detail man's knowledge of the product he represents be constantly reviewed as well as updated. This phase of the sales representative's education should be a major responsibility of the medical department of the pharmaceutical company.

I am certain that most of these companies take special care to give their detail men a great deal of information about the products they produce—information about indications, contraindications, side effects and precautions. Yet, although most of the detail men are well informed, some, unfortunately, are not. It might be helpful if sales representatives were reassessed every few years to determine whether or not they are able to fulfill their important function. Incidentally, I feel the same way about periodic assessments of everyone in the health care field, whether they be general practitioners, surgeons or salesmen.

Value of Sampling

I personally am in favor of limited sampling. I do not use sampling in order to perform clinical testing of a drug. I feel that drug testing should rightly be left to the pharmacology researcher and to the large teaching institutions where such testing can be done in a controlled environment.

I do not use samples as a "starter dose" for my patients. I do, however, find samples of drugs to be of value in that they permit me to see what the particular medication looks like. I get to see the various forms of the particular medication at first hand, and if it is in a liquid form I take the time to taste it. In that way I am able to give my patients more complete information about the particular medications that I prescribe for them.

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city they are indeed useful; cularly in the fact that they minate broadly based educa- material and serve not just ushers" of their drugs.

ther Side of the Coin

Obviously, the pharmaceuti- mpanies are not producing all aterial as a labor of love— re in the business of selling cts for profit. In this regard nbitious and improperly moti- sales representative can a negative influence on the cing physician, both by pre- ng a one-sided picture of his ct, and by encouraging the tioner to depend too heavily ugs for his total therapy. In ways, the salesman has often ted objective reality and mined his potential role as an tor.

dustry Responsibility

Since the detail man must be rmation resource as well as esentative of his particular aceutical company, he d be carefully selected and thoroughly trained. That training, perforce, must be an ongoing one. There must be a continuing battle within and with the pharmaceutical industry for high quality not only in the selection and training of its sales representatives, but also in the development of all of its promotional and educational material.

The industry must be ready to accept constructive as well as corrective criticism from experts in the field and consumer spokesmen, and be willing to accept independent peer review. The better educated and prepared the salesman is, the more medically accurate his materials, the better off the pharmaceutical industry, health professionals and the public—*i.e.*, the patients—will be.

Physician Responsibility

The practicing physician is in constant need of up-dated information on therapeutics, including drugs. He should and does make use of drug information and answers to specific questions supplied by the pharmaceutical representative. However, that information must not be his main source of continuing education. The practitioner must keep up with what is current by making use of scientific journals, refresher courses, and information received at scientific meetings.

The practicing physician not only has the right, but has the responsibility to demand that the pharmaceutical company and its representatives supply a high level of valid and useful information. I feel certain that if such a high level is demanded by the physician as well as the public, this demand will be met by an alert and concerned pharmaceutical industry.

From my experience, my impression is that sectors of the pharmaceutical industry are indeed ethical. I challenge the industry as a whole to live up to that word in its finest sense.

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

P·M·A

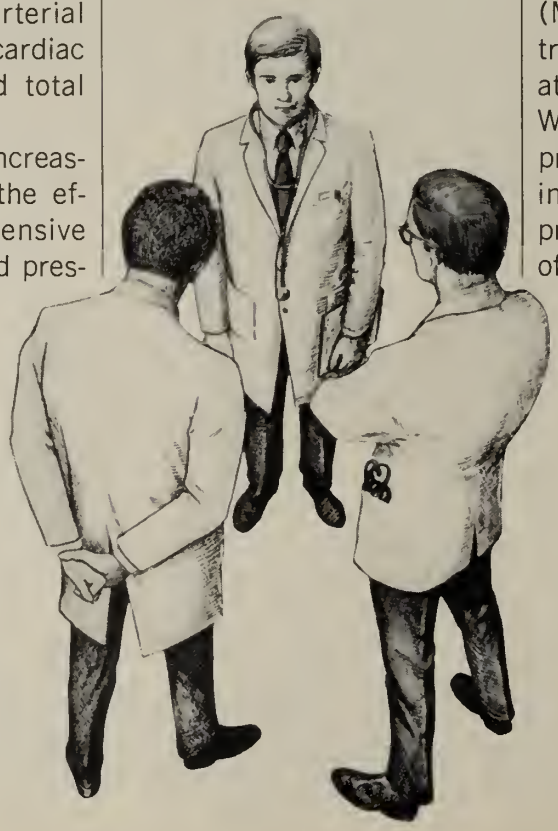
The more physicians consider the hemodynamics of lowering blood pressure...

Most physicians now agree on the importance of reducing blood pressure in the hypertensive patient. But high blood pressure exists, of course, only as part of a complete clinical picture. The hemodynamic profile of well-established essential hypertension is characterized by elevated arterial blood pressure, normal cardiac output, and increased total peripheral resistance.

And so, physicians are increasingly concerned with the effects of an antihypertensive agent not only on blood pressure itself but also on the hemodynamic pattern—in short, with the total effect of the drug. *Does* it indeed help lower blood pressure effectively? *Is* peripheral resistance reduced? *Are* cardiac output and renal functions maintained? And, also, is there likely to be drug-induced postural hypotension serious enough to pose a threat to the patient's cerebrovascular status?

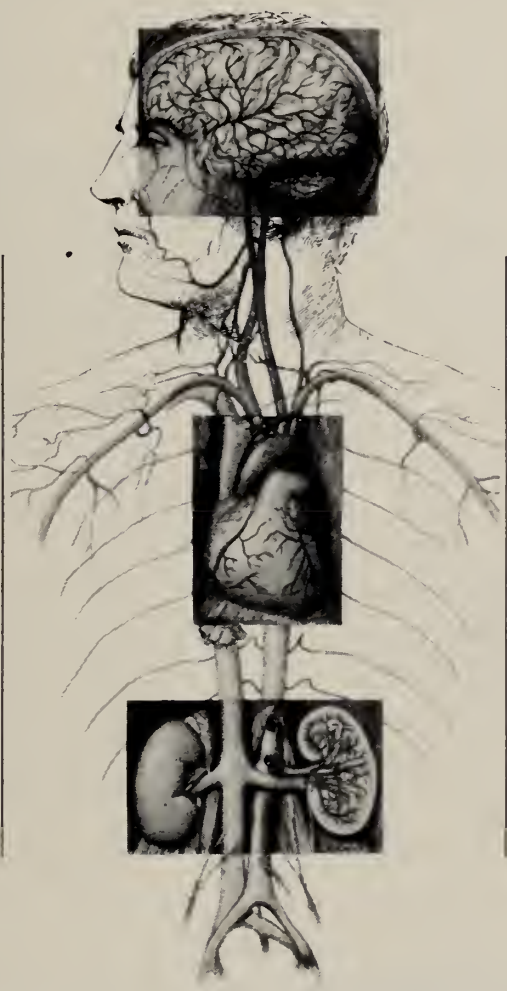
With this emphasis on overall drug performance has come a growing reliance on ALDOMET® (Methyldopa, MSD) in the treatment of sustained moderate hypertension.

With its unique hemodynamic profile, ALDOMET has drawn increasing attention and approval from physicians. First, of course, for its efficacy in



the more physicians rely on this unique antihypertensive

wering blood pressure. But ere are other considerations s well. Cardiac output is usuly maintained with no cardiac cceleration; in some patients e heart rate is actually owed. Peripheral resistance apparently reduced. LDOMET does not usually ompromise existing renal nction; it generally does not duce renal blood flow, glorular filtration rate, or filation fraction. And ALDOMET ually does not cause symptoatic postural or exercise potension.



Contraindications include active hepatic disease and known sensitivity to the drug. Use with caution in patients with a history of liver disease or dysfunction. Not recommended in pheochromocytoma or pregnancy.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

In most cases of sustained moderate hypertension

TABLETS, 250 mg and 500 mg

ALDOMET®

(METHYLDOPA | MSD)

smoothly lowers blood pressure

NEW now available in 500 mg TABLETS as well as the standard 250-mg tablets

a brief summary of prescribing information, ase see following page.

In most cases of sustained moderate hypertension

ALDOMET® (METHYLDOPA MSD)

smoothly lowers blood pressure

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis. Known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between six and twelve months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at six and twelve months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first six to twelve weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur.

Use in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Methyldopa may interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has occurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure are occasionally seen and include dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency. Angina pectoris may be aggravated. Symptoms of orthostatic hypotension may occur; if symptoms occur, reduction of dosage is suggested. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distention, constipation, flatus, and diarrhea occur occasionally; these generally can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently and are relieved by administering a thiazide diuretic; if edema progresses or signs of pulmonary congestion appear, discontinue drug. A rise in BUN has been observed. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, Bell's palsy, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Note: Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Maximal recommended daily dose is 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

How Supplied: Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

addendum

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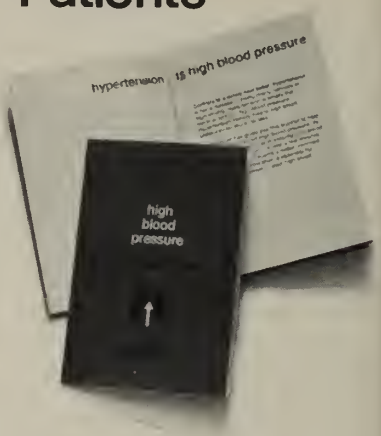
"Required Reading" For Your Hypertensive Patients



Because of the importance of patient motivation, Merck Sharp & Dohme offers "High Blood Pressure," a concise, pocket-sized booklet that defines the patient's own role in the management of hypertension. This booklet is available for you to give to your patients. It is designed to reinforce your explanation of hypertension and it emphasizes the importance of patient understanding in adhering to the regimen you prescribe.

Please ask your Merck Sharp & Dohme Professional Representative or write Professional Service Department, West Point, Pa. 19486 for a supply of this booklet.

BOOKS RECEIVED

'ooks received by THE WESTERN JOURNAL OF MEDICINE *are cknowledged in this column. Selections will be made for more xtensive review in the interest of readers as space permits.*

BIOMEDICAL ETHICS—Morality for the New Medicine—Kenneth Vaux, 'hD, Professor of Ethics, Baylor College of Medicine and Acting Director, nstitute of Religion and Human Development, Texas Medical Center, louston. Harper & Row, Publishers, Inc., 10 East 53rd Street, New York ity (10022), 1974. 128 pages, $5.95.

CURRENT PEDIATRIC DIAGNOSIS & TREATMENT—Third Edition—C. enry Kempe, MD, Professor of Pediatrics, University of Colorado School f Medicine, Denver; Henry K. Silver, MD, Professor of Pediatrics, Uniersity of Colorado School of Medicine; Donough O'Brien, MD, Professor f Pediatrics, University of Colorado School of Medicine; and Associate uthors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 974. 1020 pages, $12.00.

FITNESS, HEALTH, AND WORK CAPACITY: International Standards for ssessment—Editor: Leonard A. Larson, PhD, Director of the Department Physical Education for Men, University of Wisconsin, Madison. Macillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 974. 593 pages, $14.95.

DRUG ISSUES IN GEROPSYCHIATRY—Edited by William E. Fann, MD, Director, Clinical Research Unit, Department of Psychiatry, Veterans Administration Hospital, Durham, North Carolina, Scientific Associate, Center for the Study of Aging and Human Development, Associate Professor of Psychiatry, Duke University Medical Center; and George L. Maddox, PhD, Director, Center for the Study of Aging and Human Development, Head, Division of Medical Sociology, Department of Psychiatry, Duke University Medical Center. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1974. 122 pages, $5.95 (Paperback).

ENDOCRINOLOGY OF THE GUT—Edited by William Y. Chey, MD, DSc, Professor of Medicine, University of Rochester, School of Medicine and Dentistry, Director, Isaac Gordon Center for Digestive Diseases, Rochester, New York; and Frank P. Brooks, MD, DSc, Professor of Medicine and Physiology, University of Pennsylvania School of Medicine. Charles B. Slack, Inc., 6900 Grove Road, Thorofare, NJ (08086), 1974. 373 pages, $20.00.

FAITH HEALING: FINGER OF GOD?, OR SCIENTIFIC CURIOSITY?—An Unexpected Medical Look at the Role of Faith in Healing—Compiled by Claude A. Frazier, MD. Thomas Nelson Inc., New York, 1973 (Copewood and Davis Sts., Camden, NJ 08103). 192 pages, $5.95.

PRINCIPLES OF DRUG ACTION: The Basis of Pharmacology—Second Edition—Avram Goldstein, MD, Lewis Aronow, PhD, and Sumner M. Kalman, MD, Professors of Pharmacology, Stanford University School of Medicine, Stanford, California. John Wiley & Sons, Inc., Publishers, 605 Third Avenue, New York City (10016), 1974. 854 pages, $21.50.

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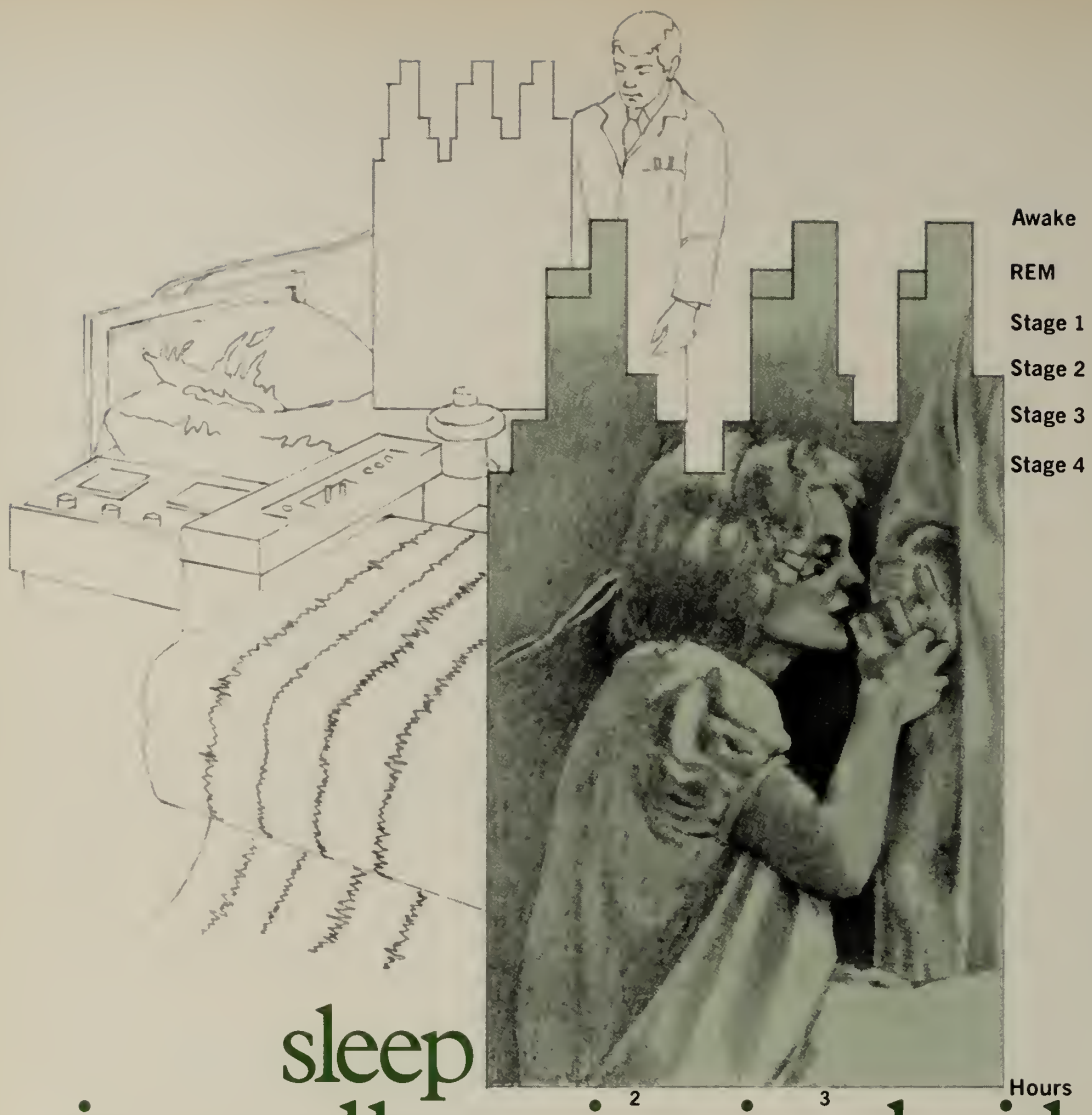

sleep is usually maintained with fewer nighttime awakenings...

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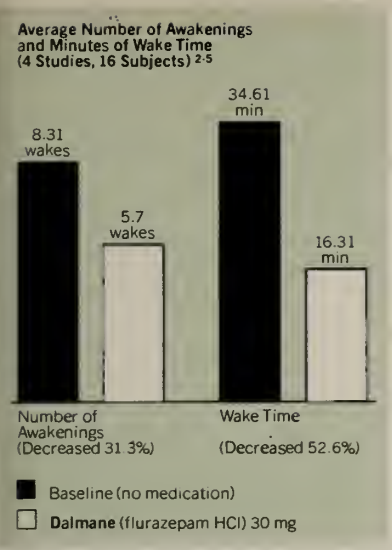
(flurazepam HCl) proved by a 17-night clinical study in the sleep research laboratory evaluating effectiveness in insomnia patients[1]

Eight patients received no medication on nights 1-4; Dalmane (flurazepam HCl or placebo on nights 5-9; crossover capsule, nights 10-14; and no medication, nights 15-17. While placebo had no significant effect on sleep maintenance, Dalmane reduced nighttime awakenings by 55.1% when given on nights 5-9, 43.7% on nights 10-14. When four control subjects received placebo on the 10 "drug" nights, awakenings *increased* 11.5% over baseline.[1]



confirmed by clinical studies in four geographically separated sleep research laboratories[2-5]

Using a 14-night protocol, involving eight insomniac and eight normal subjects, four studies confirmed the sleep-maintaining effectiveness of Dalmane (flurazepam HCl) and the reproducibility of this response. On average, one 30-mg capsule reduced number of awakenings by 31.3% and wake time by 52.6%. In all these studies, Dalmane induced sleep rapidly, on average within 17 minutes; reduced nighttime awakenings; and provided, on average, 7 to 8 hours of sleep without repeating dosage.[2-5]

Dalmane (flurazepam HCl) induces and maintains sleep, with relative safety

Dalmane is generally well tolerated; morning "hang-over" has been relatively infrequent. While dizziness, drowsiness, lightheadedness and the like have been noted most often, particularly in the elderly and debilitated, physicians should be aware of the possibility of more serious reactions, as noted in the Complete Product Information.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

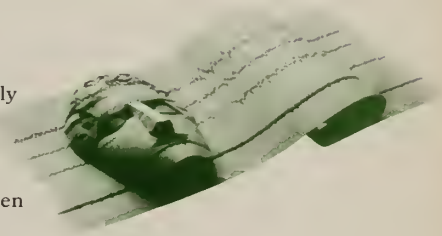
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.



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One 30-mg capsule *h.s.* — usual adult dosage (15 mg may suffice in some patients).
One 15-mg capsule *h.s.* — initial dosage for elderly or debilitated patients.

- **induces sleep within 17 minutes, on average**
- **reduces nighttime awakenings**
- **sustains sleep 7 to 8 hours, on average, without repeating dosage**

REFERENCES: 1. Kales J, *et al*: *Clin Pharmacol Ther 12*:691-697, Jul-Aug, 1971
2. Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-7, 1971
3. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ
4. Vogel GW: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ
5. Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ

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COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine**, Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

September 27-28—**Bone Cancer: The Multidiscipline Disease.** West Coast Cancer Foundation at St. Francis Hotel, San Francisco. Friday-Saturday. $75. Contact: Jerome M. Vaeth, MD, Dir., WCCF, 2200 Hayes St., San Francisco 94117.

October 2—**Urological Cancer Conference.** American Cancer Society and Los Angeles County Urological Society at Century Plaza Hotel, Los Angeles. Wednesday. Contact: William H. Tanner, Dir., Professional Ed., ACS, 2932 Wilshire Blvd., Santa Monica. (213) 828-7474.

October 25—**Leukemia—Advances in Causation, Diagnosis and Treatment.** Leukemia Society and UCSF at UCSF. Friday. 7 hrs. $25. Contact: Leukemia Society of America, Inc., Bay Area Chapter, 323 Geary St., San Francisco 94102.

November 11-12—**Franz Buschke Lectureship—2nd Annual.** UCSF. Monday-Tuesday. Nov. 11—Heavy Particle Radiation Therapy; Nov. 12—Hyperthermia in Cancer Therapy. Contact: Glenn E. Sheline, MD, Div. of Radiation Oncology, UCSF.

November 14-15—**Recent Advances in Hematology and Medical Oncology.** See Medicine, November 14-15.

November 15-16—**Current Concepts in the Diagnosis and Treatment of the Hidden Malignancies: The Intra-Abdominal Cancers.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. Contact: Dept. of Cont. Education, Mt. Zion Hospital, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 108.

December 8—**Slide Seminar on Tumors of the Gastro-Intestinal Tract.** California Tumor Tissue Registry at Century Plaza Hotel, Los Angeles. Sunday. Contact: Weldon K. Bullock, MD, Exec. Dir., Calif. Tumor Tissue Registry, L.A. County/USC Medical Ctr., 1200 N. State St., Box 40, L.A. 90033. (213) 225-3131, ext. 71820.

Continuously—**Tumor Conference.** Cruden Education Center, St. John's Hospital, Oxnard. Fridays, 12:00 noon-1:00 p.m. Advice and consultation from specialists in surgical, medical, radiotherapeutic, chemotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Cancer program has 3 year accreditation from American College of Surgeons. Contact: D. Gordon Johnston, MD, Dir. of Med. Ed., St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 266.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists (UCLA faculty members) in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John R. Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

September 19-21—**The Relevance of Animal Models to Human Dermato-Pharmacology and Dermato-Toxicology.** UCSF. Thursday-Saturday. 11 hrs. $200.

September 21—**Course in Armchair Allergy.** PMC. Saturday.

September 28-29—**Dermatologic Surgery.** See Surgery, September 28-29.

October 2-3—**American Heart Association, Greater Los Angeles Affiliate—42nd Annual Fall Symposium.** Hilton Hotel, Los Angeles. Wednesday-Thursday. $55 for members; $75 nonmembers. Contact: LaVerna Titus, AHA, Greater Los Angeles Affiliate, 2405 W. 8th St., L.A. 90057. (213) 385-4231.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: Glacier Bay, May 25-27, 1975.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: Los Angeles Convention Center, Los Angeles, February 22-26, 1975.

Hawaii Medical Association—510 S. Beretania St., Honolulu 96813. Annual Meeting—Ilikai Hotel, Honolulu, October 28-November 2, 1974.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: Big Sky of Montana, Big Sky, September 12-14, 1974.

Nevada State Medical Association—3660 Baker Lane, Reno 89501. Annual Meeting: Stockmen's, Elko, September 27-29, 1974.

Oregon Medical Association—2164 SW Park Pl., Portland 97205. Annual Meeting: Hilton Hotel, Portland, September 11-15, 1974.

Washington State Medical Association—444 NE Ravenna Blvd., #108, Seattle 98115. Annual Meeting: Davenport Hotel, Spokane, September 22-25, 1974.

October 2-5—**Present Concepts in Internal Medicine.** Letterman Army Medical Center, San Francisco. Wednesday-Saturday. 24 hrs. Contact: John J. Deller, C, Dept. of Medicine, Letterman Army Med. Ctr., Presidio, San Francisco 94129. (415) 561-4275.

October 3-4—**Coronary Care.** USC. Thursday-Friday.

October 5-6—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 7-8—**Endocrine Review.** USC. Monday-Tuesday.

October 7-11—**Common Problems in Primary Care.** See Of Interest to All, October 7-11.

October 8—**Paul M. Aggeler Visiting Professor—5th Annual.** UCSF at San Francisco General Hospital. Tuesday, 11:00 a.m-12:00 noon. Judith G. Pool, Ph.D., Stanford, will talk on her research on hemophilia during a year's sabbatical at Oxford Univ. Contact: Susan Nutter, S.F. Gen. Hosp., San Francisco. (415) 648-8200, ext. 404.

October 9-11—**Symposium on Heart Disease—44th Annual.** San Francisco Heart Association at Masonic Auditorium, San Francisco. Wednesday-Friday. Contact: Lindy Abernathy, S.F. Heart Assn., 259 Geary St., San Francisco 94102. (415) 982-5753.

October 9-11—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

October 12—**Echocardiography for the Practitioner—When, Why and How.** See Radiology, October 12.

October 17-20—**California Society of Internal Medicine—Annual Meeting.** Ahwahnee Hotel, Yosemite. Thursday-Sunday. 8 hrs. Contact: Carol H. Handley, Exec. Dir., CSIM, 1412 Central Towers, 703 Market St., San Francisco 94103. (415) 362-1548.

October 18—**Recent Advances in Rheumatology.** UCD at Woodlake Inn, Sacramento. Friday.

October 18-19—**San Diego County Heart Association.** Sheraton-Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Mrs. Cathy Ware, Prog. Dir., SDCHA, 3640 Fifth Ave., P.O. Box 3625, San Diego 92103. (714) 291-7454.

October 19-20—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 24-26—**Non-Invasive Cardiovascular Procedures.** USC. Thursday-Saturday.

October 24-26—**West Coast Allergy Society—13th Annual Scientific Program.** St. Francis Hotel, San Francisco. Thursday-Saturday. 19 hrs. $25 for members; $30 non-members. Contact: Daniel K. Billmeyer, MD, Prog. Chr., 2164 S.W. Park Pl., Portland 97205. (503) 226-1555.

October 25—**Emergency Respiratory Care for Health Related Professions.** PMC. Friday.

October 25-26—**Clinical Gastroenterology.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. Contact: Williamson B. Strum, MD, Div. of Gastroenterology, Scripps Clinic & Research Foundation, 476 Prospect St., La Jolla 92037.

October 25-26—**Rheumatology.** Southern Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

November 4-13—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

November 6—**Infectious Diseases Seminar—3rd Annual.** Torrance Memorial Hospital at Sheraton Inn Hotel, Los Angeles. Wednesday. $50. Contact: Torrance Memorial Hospital, 3330 Lomita Blvd., Torrance 90509. (213) 325-9110, ext. 362.

November 8—**Developments in the Diagnosis of Contact Dermatitis.** UCSF. Friday.

November 8-10—**Practical Electrocardiography—"Chung's Approach."** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Sunday. $125. Contact: Donald K. Chung, MD, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

November 9-10—**Physiology of Respiration.** UCSF. Saturday-Sunday.

November 11-15—**Pediatric Allergy and Clinical Immunology.** See Pediatrics, November 11-15.

November 14-15—**Recent Advances in Hematology and Medical Oncology.** UCLA at Holiday Inn, Los Angeles. Thursday-Friday.

November 30-December 1—**Kidney Function.** UCSF. Saturday-Sunday.

December 2-6—**Advances in Diagnosis and Treatment in Clinical Medicine.** American College of Physicians, UCLA, and Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Friday. $140 for ACP members; $200 non-members. Contact: ACP, Registrar, Postgraduate Courses, 4200 Pine St., Philadelphia, Pa. 19104. (215) 222-8120.

December 5-7—**Advances in Heart Disease 1975.** American College of Cardiology at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

December 11—**Colloquia in Cardiology—No. 7: Echocardiography.** American College of Cardiology at Ambassador Hotel, Los Angeles. Wednesday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

December 11-13—**Exercise in Heart Disease.** USC at Honolulu. Wednesday-Friday.

Continuously—**Review of Internal Medicine.** PMC at Presbyterian Hospital, San Francisco. August 7-October 2; Wednesdays, 7-10 p.m. For physicians planning ABIM recertification exam. $25 for each session; $20 each if registered for 4 or more. Aug. 7—Infectious Diseases; Aug. 14—Cardiology; Aug. 21—Neurology; Aug. 28—Hematology; Sept. 4—Nephrology; Sept. 11—Pulmonary Diseases; Sept. 18—Gastroenterology; Sept. 25—Rheumatology; Oct. 2—Endocrinology.

Continuously—**Recertification Review Course—Internal Medicine.** USC at Louis B. Mayer Medical Teaching Center, Keith Admin. Bldg. Tuesdays and Thursdays, 7-10 p.m. April 9-October 10, 1974. Sessions will cover 9 broad topics of internal medicine; each topic will have 5 evening sessions.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Cardiology Conference/General Medical Conference.** Cruden Education Center, St. John's Hospital, Oxnard. Tuesdays, 12:00 noon-1:00 p.m. Conferences including case presentations, discussions of specific cardiology and medical problems. Contact: R. E. Liguori, MD, Dir. of Cardiovascular Laboratory, St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 256.

Continuously—**Cardiology Conferences.** San Diego County Heart Association at Sharp Hospital, San Diego. Fridays, 8-10 a.m. Contact: William Kuzman, MD, Sharp Hospital, 7901 Frost St., San Diego. (714) 277-6121. Or Mrs. Cathy Ware, SDCHA, P.O. Box 3625, San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 294-5663. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conference.** Thursdays, 8:00 p.m. **Cardiosurgical Conference.** Fridays, 2:00 p.m. UCSD at University Hospital, San Diego.

Continuously—**Medical Mortality Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Fridays, 11:30 a.m.

Continuously—**Medical Chest Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

Continuously—**Medical-Surgical G.I. Conference.** UCSD at University Hospital, 3rd floor, rm 3, San Diego. Tuesdays, 12:30 p.m.

Continuously—**Hematology Pathology/Hematology Morphology Conference.** Mondays, 11:00 a.m. **Hematology Clinical Conference.** Mondays, 12 noon. UCSD alternating between University and VA Hospitals, San Diego.

Continuously—**Gastroenterology Conference.** Tuesdays, 11:00 a.m. **Gastrointestinal Conference.** Tuesdays, 12:30 p.m. **Gastroenterology-Pathology Conference.** Wednesdays, 11:00 a.m. UCSD at University Hospital, San Diego.

(Continued on Page 44)

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing without prescription.
Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based or chemical assay—and is also biologically assayed and standardized in animals.
Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.
The ratio of T_4 and T_3 in Proloid (thyroglobulin is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when stored at usual room temperature.
Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g. cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.
In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in non emergency situations, in an attempt to reduce the size of such goiters.
Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.
Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (3 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.
Morphologic hypogonadism and nephrosis should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.
Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.
Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.
Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.
Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.
Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.
(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)
How Supplied. ¼ grain; ½ grain; scored 1 grain; 1½ grain; scored 2 grain; 3 grain; and scored 5 grain tablets, in bottles of 100 and 1000.
Full information available on request.
WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, New Jersey 07950
PR-GP-31-B/W

IN NATURAL THYROID THERAPY:

ARE PATIENTS GETTING THE POTENCY YOU PRESCRIBE?

Unlike U.S.P. desiccated thyroid, Proloid®(thyroglobulin) offers the assurance of constant potency.

To begin with, Proloid is uniquely purified. The thyroglobulin extracted from hog thyroid is devoid of any glandular debris.

Then, Proloid is chemically and biologically assayed to assure consistent metabolic activity from batch to batch. The T_4 and T_3 content of every dose is blended for optimal thyroid replacement.

Important, too, is the fact that Proloid is invariably "fresh" when your patients take it. Under proper storage conditions, its potency will not diminish for at least four years.

All of which adds up to this: the potency of Proloid is constant...for more consistent results.

PROLOID®
(thyroglobulin)

natural thyroid therapy that leaves nothing to chance

(Continued from Page 42)

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Preceptorships in Cardiology.** PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Continuously—**Preceptorships in Practical Office Dermatology.** PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Continuously—**Preceptorships in Infectious Disease.** PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Renal Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

Continuously—**Rheumatology Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. 2nd and 4th Fridays, 12:30 p.m.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of every other month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1534.

Continuously—**Training for Physicians in General Internal Medicine.** LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Dermatology. 11:00 a.m. VA Hospital, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

8:30 a.m., Auditorium, Brown Bldg., Mt. Sinai Hospital Los Angeles. UCLA.

Dermatology. 10:00 a.m. University Hospital, San Diego UCSD.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:00 noon. Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., VA Hospital, San Diego. UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD

8:00-10:00 a.m., 4th Floor, UCLA Medical Center. UCLA

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30-10:00 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m. Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

MENTAL RETARDATION

September 29-October 11—**Mental Retardation.** UCLA. 1 days.

OBSTETRICS AND GYNECOLOGY

September 19-21—**Biology and Pathology of Pregnancy and the Newborn Period.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Saturday.

October 9-11—**Fetal Monitoring.** USC. Wednesday-Friday.

October 12—**Prenatal Nutrition—Workshop for Physicians** Calif. Association for Maternal and Child Health at Sher

ton Inn, San Diego. Saturday. Contact: Carol G. Corruccini, M.S., 425 University Ave., No. 6, Davis 95616. (916) 756-8471.

ctober 14-15—**New Horizons in Perinatal Intensive Care.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. 13 hrs. $125. Contact: Bonnie Stapleton, Cont. Ed. Coord., Harbor Gen. Hosp., 1124 W. Carson, Torrance 90502. (213) 775-7711, ext. 1373.

ctober 16-19—**Ob-Gyn Review.** USC. Wednesday-Saturday.

ctober 20-23—**International Family Planning Research Association.** Gene Autry Hotel, Palm Springs. Sunday-Wednesday. Contact: Ludwig Lauerhass, Exec. Dir., 2960 W. 8th St., Los Angeles 90005. (213) 386-1970.

ovember 1—**Advances in Perinatal Care.** Northern California Obstetrical & Gynecologic Society at Host Airport Hotel, Sacramento. Friday. Contact: Solon Barbis, MD, Prog. Chr., 1816 Professional Dr., Sacramento. (916) 482-6510.

ovember 6-9—**American College of Obstetricians & Gynecologists, District VIII.** Century Plaza Hotel, Los Angeles. Wednesday-Sunday. Will reconvene Nov. 11-13 at Princess Hotel, Acapulco. Contact: ACOG District VIII, 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

ovember 22-25—**1974 Symposium of Gynecologic Endoscopy.** American Association of Gynecological Laparoscopists at Disneyland Hotel, Anaheim. Friday-Monday. Contact: Jordan M. Phillips, MD, 11239 S. Lakewood Blvd., Downey 90241. (213) 862-8181.

ontinuously—**Ob-Gyn Case Review.** Saturdays, 8:00 a.m. **Gyn Tumor Conference/Mortality Conference.** Wednesdays, 12:30 p.m. **Ob-Gyn Pathology Conference.** Wednesdays, 4:00 p.m. UCSD at University Hospital, San Diego.

ontinuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ontinuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

and Rounds—Obstetrics and Gynecology

Mondays

10:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

8:00-9:00 a.m., Fourth Floor Auditorium, UCLA Medical Center. UCLA.

5:00 p.m. Pickard Auditorium, University Hospital, San Diego. UCSD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

PEDIATRICS

October 7-11—**Common Problems in Primary Care.** See Of nterest to All, October 7-11.

ober 14-15—**New Horizons in Perinatal Intensive Care.** See Obstetrics and Gynecology, October 14-15.

ober 19-23—**American Academy of Pediatrics.** Hilton Hotel, San Francisco. Saturday-Wednesday. Contact: Robert . Frazier, MD, Exec. Dir., 1801 Hinman Ave., Evanston, ll. 60204.

November 11-15—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

December 7—**American Academy of Pediatrics, Chapter I, District IX.** San Franciscan-PSA Hotel, San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501. (415) 523-3417.

Continuously—**Fellowship in Cleft Palate.** See Surgery, Continuously.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD. Small Conference Room, University Hospital, San Diego. Fridays, 12:30 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., and Fridays, 9:30-11:00 a.m., Conference Room 3. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Fourth Thursday of each month, 2:00 p.m., Main Doheny Conference Room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Continuously—**Pediatric Immunology and Allergy Seminar.** UCSD. Wednesdays, 8:00 a.m.

Continuously—**Pediatric Neurology.** UCSD at University Hospital, 3rd floor, rm. 3, San Diego. 1st and 3rd Wednesdays, 12:30 p.m.

Continuously—**Pediatric-Radiology-Urology Conference.** UCSD at University Hospital, Radiology Conference Room, San Diego. 1st and 3rd Fridays, 4:00 p.m.

Grand Rounds—Pediatrics

Tuesdays

Pediatric Cardiology. 7:30 a.m. University Hospital, San Diego. UCSD.

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

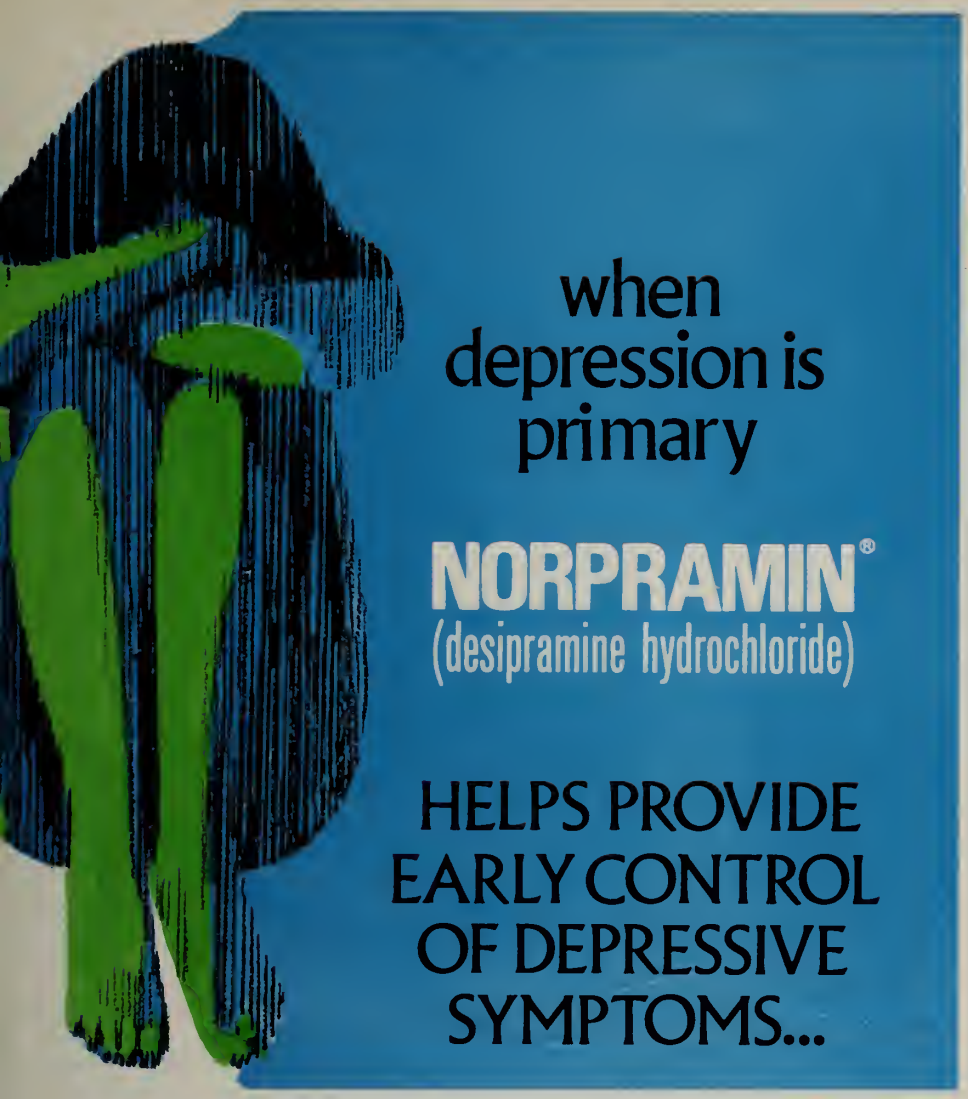
8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

(Continued on Page 48)

When you see anxiety-look for depression
NORPRAMIN
(desipramine hydrochloride)



Anxiety is an invidious symptom. It feeds upon sickness, gnaws, grows and invades every cranny of psychic pathology adding intensity to torment. Anxiety as a symptom secondary to depression may be so dominant that it obscures the primary diagnosis. It may suggest treatment with tranquilizers which often help. But as the vampire of legend had to have a laurel stake driven through its heart to truly die, so anxiety secondary to depression will not cease to nibble and bite until an antidepressant eradicates the primary illness—and symptomatic anxiety starves.

IN BRIEF:

Indications: Norpramin® (desipramine hydrochloride) is indicated for the relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contraindications: Desipramine hydrochloride should not be given within two weeks of treatment with a monoamine oxidase inhibitor. Contraindications include the acute recovery period following myocardial infarction and hypersensitivity to the drug. Cross sensitivity with other dibenzazepines is a possibility.

Warnings: 1. Extreme caution should be used in patients: (a) with cardiovascular disease, (b) with a history of urinary retention or glaucoma, (c) with thyroid disease or those on thyroid medication, (d) with a history of seizure disorder. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. *Use in Pregnancy:* Safe use during pregnancy and lactation has not been established. 4. *Use in Children:* Norpramin® (desipramine hydrochloride) is not recommended for use in children. 5. This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Therefore, the patient should be cautioned accordingly.

Precautions: This drug should be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with drugs of this class. If possible, dispense in child-resistant containers. It should be kept out of reach of children. Reduce dosage, or alter treatment, if serious adverse effects occur. Norpramin® (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates and may cause exacerbation of phychosis in schizophrenic patients. Use cautiously with anticholinergic or sympathomimetic drugs. Response to alcoholic beverages may be exaggerated. In the concurrent administration of ECT and antidepressant drugs one should consider the possibility of increased risk relative to benefits. Discontinue as soon as possible prior to elective surgery because of possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is neutropenia.

Adverse Reactions: *Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. *Psychiatric:* confusional states (especially in the elderly), hallucinations, disorientation, delusions; anxiety, agitation; insomnia and nightmares; hypomania; exacerbation of phychosis. *Neurological:* paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, hypotonic bladder. *Allergic:* skin rash, petechiae, urticaria, itching, photosensitization, edema (of face and tongue or general), drug fever. *Hematologic:* agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue. *Endocrine:* gynecomastia; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels. *Other:* jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia. *Withdrawal Symptoms:* Though not indicative of addiction, abrupt cessation after prolonged therapy may produce nausea, headache and malaise.

Dosage and Administration: *The usual adult dose:* 50 mg. three times daily; increase if necessary after 7 to 10 days to maximum of 200 mg. daily. Dosages above 200 mg. per day are not recommended. *Maintenance:* At a lower dose adequate to maintain remission. *Adolescent and geriatric patient dose:* 25 to 50 mg. daily if necessary.

Overdosage: There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug. The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure and regulation of fluid- and acid-base balance are well known in most medical centers. If heart failure is imminent, digitalize promptly.

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Division of Colgate-Palmolive Company

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LAKESIDE LABORATORIES, INC.
Milwaukee, Wisconsin 53201

(Continued from Page 45)

Pediatric Infectious Disease. 1:30 p.m. University Hospital, San Diego. UCSD.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:30 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., 5th floor Ward, St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

October 24-27—**American Academy of Child Psychiatry.** Fairmont Hotel, San Francisco. Thursday-Sunday. Contact: American Academy of Child Psychiatry, 1800 R Street, NW, Washington, D.C. 20009.

November 7-8—**Community Alternatives to State Hospital Treatment.** UCD. Thursday-Friday.

December 13—**Psychological Aspects of the Rehabilitation of Patients with Industrial Back Injuries.** PMC. Friday.

Continuously—**Center for Training in Community Psychiatry —Fall Program.** 17 courses offered. Application deadline is September 20, 1974. Contact: Center for Training in Community Psychiatry, 11665 W. Olympic Blvd., Los Angeles 90064. (213) 478-1535.

Continuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Seminar in Ambulatory Methods.** UCSD at Mental Health Clinic, San Diego. Mondays, 11:00 a.m.

Continuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

Grand Rounds—Psychiatry

Tuesdays

8:30 a.m. VA Hospital, Rm. 2010, San Diego. UCSD.

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, Sa Francisco.

RADIOLOGY AND PATHOLOGY

September 22-23—**Society for Pediatric Radiology.** Hilton Hot San Francisco. Sunday-Monday. Contact: John P. Dorst, MI Johns Hopkins Hospital, Baltimore, Md. 21205.

September 24-27—**American Roentgen Ray Society.** Hilt Hotel, San Francisco. Tuesday-Friday. Contact: Ted F. Leig MD, Emory University Clinic, Atlanta, Ga. 30322.

September 28—**Radiology of the Kidney.** Southern Cal Permanente Medical Group at Hyatt Regency Hotel, L Angeles. Saturday. Contact: Shirley Gach, So. Calif. P manente Med. Group, 4900 Sunset Blvd., L.A. 90027. (21 667-4242.

October 12—**Echocardiography for the Practitioner—Wh Why and How.** Memorial Hospital Medical Center - U Center for Health Education, Long Beach. Saturday. $ Contact: Exec. Sec., Center for Health Education, 28 Atlantic Ave., Long Beach 90801. (213) 595-3823.

October 25-26—**Society of Nuclear Medicine, Northern Southern California Chapters—Annual Meeting.** Hilt Hotel, San Francisco. Friday-Saturday. Contact: Society Nuclear Medicine, No. Calif. Chapter, 1595 Soquel D Santa Cruz. (408) 476-7300.

November 2—**Laboratory Evaluation of Thyroid Diseas** PMC. Saturday.

November 9-10—**Adult Cardiac Radiology.** UCLA. Saturd Sunday.

November 11-12—**Franz Buschke Lectureship.** See Can November 11-12.

November 16-17—**American Association for Electromyogra and Electrodiagnosis.** St. Francis Hotel, San Francisco. urday-Sunday. Contact: W. C. Wiederholt, MD, Sec., 7 Via Valverde, La Jolla 92037. (714) 459-8443.

Continuously—**Nuclear Medicine Conference.** Radiology Cl room, St. John's Hospital, Oxnard. Mondays, 12:00 no 1:00 p.m. Cases reviewed and discussed. Advice and con tation from specialists in the practice of nuclear medic techniques. Contact: Michael Lopiano, MD, Dir. of Nuc Med. Dept., St. John's Hospital, 333 N. "F" St., Oxn 93030. (805) 483-1141, ext. 297.

Continuously—**Ob/Gyn Correlated Pathology Conference.** Mary's Hospital, San Francisco. Mondays, 12:00 noon, S Lounge. Contact: Charles H. Lithgow, MD, Dir. of Med Education, St. Mary's Hospital, 2200 Hayes St., San F cisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's H pital, San Francisco. 2nd and 4th Wednesdays. Cont Charles H. Lithgow, MD, Dir. of Medical Education, Mary's Hospital, 2200 Hayes St., San Francisco 94117. (752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San F cisco. Mondays, 8:00-9:00 a.m., Clinic Building, Roo Contact: Charles H. Lithgow, MD, Dir. of Medical Ed tion, St. Mary's Hospital, 2200 Hayes St., San Franc 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's pital, San Francisco. Third Tuesday of each month, 9 10:00 a.m., Morrissey Hall. Contact: Charles H. Lith MD, Dir. of Medical Education, St. Mary's Hospital, Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Or County Radiology Society and Orange County Medical ter at Orange County Medical Center, Orange. 1st Tue of each month, September-June, 7:30-9:00 p.m. Con Edward I. Miller, MD, 301 Newport Blvd., Newport B (714) 645-8600.

ontinuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

ontinuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

ontinuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

ontinuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

ontinuously—**Medical X-Ray Conference.** Monday-Friday, 9:30 a.m. (Wednesdays, 8:30 a.m.). **Diagnostic X-Ray Review.** Wednesdays, 3:30 p.m. UCSD at University Hospital, San Diego.

ontinuously—**Radiology/Pathology Conference.** UCSD at University Hospital, Pickard Amphitheatre, San Diego. Thursdays, 12:30 p.m.

ontinuously—**G.I. Radiology Conference.** Fridays, 1:00 p.m. **Pediatric Radiology Conference.** Thursdays, 4:30 p.m. UCSD at University Hospital, San Diego.

ontinuously—**Neuroradiology Conference.** UCSD at University Hospital, San Diego, Tuesdays, 4:30 p.m. and at VA Hospital, San Diego, Wednesdays, 2:00 p.m.

Continuously—**Ortho-Radiology Conference.** UCSD at VA Hospital, San Diego. Fridays, 8:00 a.m.

Continuously—**Radiology-Urology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 3:30 p.m.

Continuously—**Pathology Review.** Wednesdays, 9:30 a.m. **Cardiovascular Pathology Conference.** Tuesdays, 8:00 a.m. **Pathology-Urology Conference.** Alternate Mondays, 4:30 p.m. UCSD at University Hospital, San Diego.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

September 21—**Orthopaedic Surgery and Surgical Anatomy of the Spine.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital, L.A. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Ed. Committee, ICS, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

September 26-28—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

September 26-28—**Cerebral Palsy—New Perspectives.** American Academy for Cerebral Palsy at Children's Hospital at Stanford. Thursday-Saturday. $75. Contact: E. E. Bleck, MD, Children's Hospital at Stanford, 520 Willow Rd., Palo Alto 94304.

Cordial Invitation

We, Mexican MDs, are glad to invite our American colleagues to a joint venture at a Hotel-Club in Mazatlán, Sinaloa, Mexico

The "Asociación de Médicos Mexicanos, A.C." is carrying on a project named **"Ammaczatlán,"** based on the construction of a Hotel-Club in Mazatlán. We actually have a lot on the beach, located between the Camino Real and the Holiday Inn hotels.

Our Hotel-Club will have 40 air-conditioned apartments with two bedrooms, living-dining room, bathroom and kitchenette.

There will be a swimming pool, splash pool, garden and a parking lot.

Our shareholders will be able to reside there as many days as shares they own—paying only the service-maintenance fee, which, according to an economic study made, will be about $14 a day.

The price of the share ($110) is established by its nominal value ($100) and a premium ($10) for organization expenses. Until the shares subscription is completed, the share nominal will be deposited in the joint savings account which our Association has in Financiera Comermex and it will accumulate 8.374% annual interest, with capitalization every three months. If the promotion should fail, the shareholders' money, plus the accumulated interest, will be returned to them.

We request from our American colleagues who may be interested in this joint venture to fill out the coupon below and send it back to us.

Asociación de Médicos Mexicanos, A.C.
Leandro Valle No. 93 Nte.
Torreón, Coah.
México.

I am interested in the "Ammaczatlán" Hotel-Club project. Please send illustrated pamphlet to:

(PLEASE PRINT)

NAME_____

ADDRESS_____

CITY_____ STATE_____ ZIP_____

Signature_____

September 26-28—**The Neck.** American Academy of Orthopaedic Surgeons. Anaheim. Thursday-Saturday. $150 for physicians; $50 residents. Contact: E. Shannon Stauffer, MD, Rancho Los Amigos Hospital, Downey 90242.

September 28-29—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

October 5-12—**Western Orthopedic Association.** Hawaii. One week. Contact: Ms. H. Jacqueline Martin, Exec. Sec., WOA, 354 21st St., Oakland 94612.

October 17-18—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 17-19—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

October 18-19—**Society for Ear, Nose, and Throat Advances in Children.** San Francisco. Friday-Saturday. Contact: Jack L. Paradise, MD, Sec.-Treas., 125 De Soto St., Pittsburgh, Pa. 15213.

October 19—**Surgical Anatomy and Surgery of Total Hip Replacement.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital, L.A., Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Ed. Committee, ICS, 5351 Tampa Ave., Tarzana 91356. (213) 344-3305.

October 28-November 1—**Association of Military Surgeons of the United States—81st Annual Meeting.** Town and Country Hotel, San Diego. Monday-Friday. Contact: Lt. Commander Thomas E. Thomas. MSC USN, Military Personnel Dept., Naval Regional Medical Center, San Diego 92134. (714) 233-2022.

October 31-November 1—**Strabismus.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday.

November 8—**Orthopedic Symposium—Arthroplasties of the Knee.** Southern Calif. Permanente Medical Group at Sheraton Hotel, Anaheim. Friday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., L.A. 90027. (213) 667-4242.

November 9—**Orthopaedic Surgery and Surgical Anatomy of the Lower Extremity.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital, L.A., Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Ed. Committee, ICS, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

November 14-15—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

November 14-16—**Phaco-Emulsification.** St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

November 16-17—**American Society of Anesthesiologists—Regional Refresher Course.** Riviera Hotel, Palm Springs. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068.

November 20-23—**Western Surgical Association—Annual Meeting.** Union Square Hyatt, San Francisco. Wednesday-Saturday. Contact: William P. Mikkelson, MD, 1127 Wilshire Blvd., Los Angeles 90017.

November 21-23—**Management of Acute Hand Injuries.** USC and American Academy of Orthopaedic Surgeons at USC. Thursday-Saturday. Contact: USC or Arthur H. Osborne, MD, 3314 Rancho Rio Bonita Rd., Covina 91724.

December 4-6—**Advise and Dissent in Glaucoma—Annual Ophthalmology Course.** UCSF at Union Square Hyatt, San Francisco. Wednesday-Friday.

December 6-8—**Electronystagmography.** PMC at Sheraton Palace Hotel, San Francisco. Friday-Sunday.

December 11-14—**Fluorescein Angiography and Photocoagulation in Macular and Retinal Vascular Disease.** USC. Wednesday-Saturday.

December 12-13—**Phaco-Fragmentation.** UCSF. Thursda Friday.

December 12-14—**Phaco-Emulsification.** St. John's Hospi and Southern Calif. Lions Eye Institute at St. John's Ho pital, Santa Monica. Thursday-Saturday. Contact: Robert M Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 904

December 14—**Orthopaedic Surgery and Surgical Anatomy the Neck and Upper Extremity.** International College Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, L Angeles. Saturday. $50. 8 hrs. Contact: Irving Rehman, Ph Chairman, Postgraduate & Ongoing Education Committe 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

December 15—**Clinical Disorders of the Pelvis.** UCLA a Granada Community Hospital at Calif. State Univ., Nor ridge. Sunday. Contact: Rose Degraffenreid, Granada Co munity Hosp., 10445 Balboa Blvd., Granada Hills 913 (213) 360-1021, ext. 730.

Continuously—**Fellowship in Cleft Palate.** Rancho Los Amig Hospital, Downey. One-year fellowship in the total evaluati and management of cleft lip and cleft palate patients. Co tact: Libby Wilson, MD, Rancho Los Amigos Hosp., 76 E. Imperial Highway, Downey 90242. (213) 922-7454.

Continuously—**Anesthesia Lecture Series.** UCSD at Univers Hospital, 3rd floor conference room, San Diego. Wedn days, 4:45 p.m.

Continuously—**Anesthesiology Mortality and Morbidity Co ference.** UCSD at VA Hospital, Rm. 6006, San Die Thursdays, 4:30 p.m.

Continuously—**Neurological Sciences.** St. Francis Hospit Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of rad logical evaluations and pathological specimens of curr material and review of current topics in specialty. Wee notification of cases available. Contact: Ralph Miller, A min. Asst., St. Francis Hospital, 3630 Imperial Highw Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Science Lecture Series.** Dept. of Surge St. Mary's Hospital, San Francisco. Mondays, 11:15 a. 12:15 p.m., Morrissey Hall. Contact: Charles H. Lithg MD, Dir. of Medical Education, St. Mary's Hospital, 22 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Pd graduate traineeships of 4-14 days duration, as you wish. tuition but donations accepted. Contact: Orthopaedic Di sion, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser S Francisco, and Harkness Memorial Hospitals. Third Tu day of each month, 6:00 p.m. Contact: Charles H. Lithg MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at Angeles County-USC Medical Center. Mondays, 7:00-9 p.m. Contact: Dept. of Orthopedics, USC School of M 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UC By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arra ment.

Continuously—**Training for Physicians in Nephrology.** CR Area VI and LLU at LLU. Courses of four weeks or m available, to be scheduled by arrangement. Hemodial peritoneal dialysis, renal biopsy, and kidney transplantat 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. C room. Contact: Charles H. Lithgow, MD, Dir. of Med. St. Mary's Hospital, 2200 Hayes St., San Francisco 94 (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Mortality and Morbidity Conference.** UCSD alternating between University and VA Hospitals, San Diego. Saturdays. 9:30 a.m.

Continuously—**Ortho Surgical Conference.** UCSD at University Hospital, 3rd floor conference room, San Diego. Wednesdays, 8:00 a.m.

Continuously—**Otolaryngology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Fridays, 8:30 a.m.

Continuously—**Laryngeal Physiology.** UCSD at VA Hospital, San Diego. Fridays, 8:30 a.m.

Continuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Trauma Conference.** UCSD at University Hospital, 1st floor conference room, San Diego. Tuesdays, 3:30 p.m.

Continuously—**Vascular Surgery Conference.** UCSD alternating between VA and University Hospitals, San Diego. Thursdays, 4:00 p.m.

Continuously—**Radiology-Urology Conference. Pathology-Urology Conference.** See Radiology and Pathology, Continuously.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Lebanon Hall Auditorium, Cedars-Sinai Hospital, Los Angeles. UCLA.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery.** 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Otolaryngology. 12:00 noon. University and VA Hospitals, San Diego. UCSD.

Neurology, Neuropathology, Neurosurgery. 4:00 p.m. University and VA Hospitals, San Diego. UCSD.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital, 1st, 3rd, 5th Sat.; VA Hospital, 2nd, 4th Sat., San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

Orthopedic Surgery. 8:00-9:00 a.m. UCSF. September 14-February 22, 1975. Subjects to be announced.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

September 21-December 1—**A Basic Course in Acupuncture.** Pacific Hospital, Long Beach. 12 sessions; Saturdays and Sundays, every other week. $1,100. Contact: Jane F. Lee, MD, 909 Hyde St., San Francisco. (415) 474-2677; or George Wong, Jr., MD, 911 E. San Antonio Dr., Ste. 102. Long Beach 90807. (213) 422-1261.

September 27-28—**The Role of Nutrition in Medicine.** UCD. Friday-Saturday.

October 1—**Prevention, Diagnosis and Management of Stroke.** American Geriatrics Society, Western Division, at Hilton Hotel, Los Angeles. Tuesday. $25. Contact: Richard M. Johnson, MD, Sec., 211 Cherry Ave., Long Beach 90802.

October 3-5—**American Medical Writers Association—34th Annual Meeting.** Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. Contact: American Medical Writers Assn., 9650 Rockville Pike, Bethesda, Md. 20014.

October 7-9—**California Hospital Association—Annual Meeting.** Town and Country Hotel, San Diego. Monday-Wednesday. Contact: CHA, 925 L St., Ste. 1250, Sacramento 95814. (916) 443-7401.

October 7-11—**Primary Care.** STAN. Monday-Friday. A review course for general practitioners, family practitioners, gen. internists and gen. pediatricians.

October 10-12—**Western Industrial Health Conference—18th Annual.** Western Industrial Medical Association at Hilton Hotel, Los Angeles. Thursday-Saturday. Contact: Mr. B. H. Bravinder, Exec. Sec., P.O. Box 201, Alamo 94507. (415) 837-0874.

October 12—**Hypertension.** USC. Saturday.

October 14-17—**American Academy of Family Physicians—Annual Scientific Assembly.** Los Angeles Convention Center. Monday-Thursday. Contact: Edward E. Daleske, Sec., Comm. on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, Mo. 64114. (816) 333-9700.

October 18—**Dimensions of Human Relatedness.** Kings View Hospital at Towne House, Fresno. Friday. $35. Contact: Julie Fernandez, Kings View Hospital, 42675 Road 44, Reedley 93654.

October 19—**Fluid and Electrolyte Symposium.** St. Mary Medical Center, Long Beach. Saturday. 6 hrs. $50. Contact: Dept. of Medical Education, St. Mary Medical Center, P.O.

Box 887, 1050 Linden Ave., Long Beach 90801. (213) 435-4441, ext. 425.

October 23—**Ethical Aspects of Experimentation with Human Subjects.** USC. Wednesday.

October 28-November 1—**Intensive Care.** STAN. Monday-Friday.

October 28-November 2—**Hawaii Medical Association.** Ilikai Hotel, Honolulu. Monday-Saturday. Contact: Mr. H. Tom Thorson, Exec. Dir., 510 S. Beretania St., Honolulu 96813.

November 1-2—**Thy Brother's Keeper.** USC. Friday-Saturday.

November 1-3—**The Patient—Our Ultimate Concern.** Calif. Society of Hospital Pharmacists, Calif. Hospital Assn., CMA, Calif. Nursing Assn., Calif. Pharmaceutical Assn. at Marriott Hotel, Los Angeles. Friday-Sunday. Contact: Kenneth N. Horowitz, Pharm. D., Centinela Valley Community Hospital, 555 E. Hardy St., Inglewood 90301.

November 3-6—**American Society of Tropical Medicine and Hygiene—23rd Annual Meeting.** Princess Kaiulani, Honolulu. Sunday-Wednesday. Contact: George R. Healy, PhD, P.O. Box 15208, Druid Hills Branch P.O., Atlanta, Ga. 30333. (404) 633-3311, ext. 3227.

November 6—**Infectious Diseases Seminar.** See Medicine, November 6.

November 10-13—**California Academy of Family Physicians.** Hyatt Regency Hotel, San Francisco. Sunday-Wednesday. Contact: William W. Rogers, Exec. Sec., CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 11-22—**Emergency Department Medicine in Practice.** Harbor General Hospital, UCLA, American College of Emergency Physicians at Harbor General Hospital, Torrance. Two weeks. $450. Contact: Mrs. Bonnie Stapleton, Cont. Ed. Coord., Professional Staff Assn., Harbor Gen. Hosp., 1124 W. Carson St., Torrance 90502.

November 17-22—**American Congress of Rehabilitation Medicine.** St. Francis Hotel, San Francisco. Sunday-Friday. Contact: Creston C. Herold, Exec. Dir., ACRM, 30 N. Michigan Ave., Chicago 60602.

November 19—**Association of Academic Physiatrists.** St. Francis Hotel, San Francisco. Tuesday. Contact: George H. Kraft, Sec., Dept. of Rehabilitation Medicine, Univ. of Washington, Seattle 98195.

November 29-December 1—**International College of Applied Nutrition—Fall Seminar.** International Hotel, Palm Springs. Friday-Sunday. Contact: Michael Walczak, MD, P.O. Box 386, La Habra 90631. (213) 697-4576.

December 5-6—**Air Pollution Medical Research Conference.** American Medical Association at Sheraton Palace Hotel, San Francisco. Thursday-Friday. Contact: AMA, 535 N. Dearborn St., Chicago, Ill. 60610.

December 7—**Family Practice Symposium.** Southern California Permanente Medical Group, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

Continuously—**Emergency Care.** USC. September 17-December 3. Tuesdays, 7:30-10:00 p.m.

Continuously—**Bedside Clinics.** USC. September 26-December 19. Thursdays, 7:30-9:30 p.m.

Continuously—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. October 1-December 3. Tuesdays (except Nov. 5 and 12).

Continuously—**Clinical Conferences.** UCSF at Community Hospital, Santa Cruz. October 9, 1974-June 11, 1975. Wednesdays.

Continuously—**Continuing Medical Education Noon Conferences.** The Hospital of the Good Samaritan, Los Angeles. Every weekday, 12-1 p.m. For monthly calendar, contact: Janie Sternal, Coord., Cont. Med. Ed., Hosp. of the Good Samaritan, 1212 Shatto St., Los Angeles 90029. (213) 482-8111.

Continuously—**Clinical Problems in Daily Practice: Physiological Basis and Practical Management.** UCSF at Chinese Hospital, San Francisco. 1st Tuesday of each month; 8:00-9:30 p.m. Sept.—Jaundice; Oct. & Nov.—to be announced.

Continuously—**Emergency Room Lecture Series.** UCSD at University Hospital, San Diego. Wednesdays, 10:00 a.m.

Continuously—**Endocrinology, Metabolism, Reproductive Medicine, Genetics Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 11:30 a.m.

Continuously—**Preceptorships in International Health, Microbiology, Pharmacology and Experimental Therapeutics, Physiology.** UCSF. By special arrangement.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange County Chapter, American Academy of Family Physicians at Saddleback Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; La Palma Intercommunity Hosp., La Palma; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Riviera Hosp., Torrance; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $15 per session. Contact: William J. Newman, MD, P.O. Box B, Sonoma 95476. (707) 996-3621.

Continuously—**Basic Science Seminar.** UCSD Wednesdays, 9:15 a.m., University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

Continuously—**Medical Media Network.** Programs and study guides produced in association with faculties of major medical schools and centers throughout the U.S. MMN administered by University Extension, UCLA. Rental or purchase, 16 mm, super 8 mm, videotape and video-cassette. Provides physicians with current educational programs. Contact: Ms. Jan MacAllister, Distribution Mgr., MMN, 1099 Le Conte Ave., Room 540, Los Angeles 90024. (213) 825-7781.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

September 11-15—**Oregon Medical Association 100th Annual Session.** Portland Hilton Hotel. Contact: James Kronenberg, Associate Executive Director, OMA, 2164 SW Park Place, Portland 97205.

OBSTETRICS AND GYNECOLOGY

October 6-10—**Pacific Coast Obstetric and Gynecological Society,** Bend. Contact: M. W. Breese, MD, 1133 SW Market Street, Portland 97205.

SURGERY

September 27-October 3—**International College of Surgeons, Western Hemisphere Congress,** Portland. Contact: M. L. Brodney, 1516 N Lake Shore Drive, Chicago, IL 60610.

OF INTEREST TO ALL PHYSICIANS

September 16—**What's New—Family Practice Section, Oregon Medical Association Annual Meeting.** Hilton Hotel, Portland. Contact: Oregon Academy of Family Physicians, Ms. Skippie Patterson, 2164 S.W. Park Place, Portland, 97205.

October 16-19—**American Society of Human Genetics,** Portland. Contact: W. E. Nance, MD, Medical Genetics, Indiana University Medical Center, Indianapolis, IN 46202.

November 7—**Thrombophlebitis and Thromboembolic Disease,** 9:00 a.m. to 3:30 p.m. Assembly Hall, Portland Adventist Hospital. Contact: Theodore R. Flaiz, MD, Portland Adventist Hospital, 6040 S.E. Belmont, Portland, 97215.

November 30-December 4—**American Medical Association Clinical Meeting,** Portland. Contact: Ernest B. Howard, MD, AMA, 535 N. Dearborn Avenue, Chicago, IL 60610.

WASHINGTON, MONTANA, ALASKA and IDAHO

September 22-25—**Washington State Medical Association Annual Meeting.** Davenport Hotel, Spokane. Contact: Harlan R. Knudson, Executive Director, WSMA, 444 NE Ravenna Boulevard—#108, Seattle 98115. (206) LA 3-9110.

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

September 27-28—**Arthritis Days '74.** Friday-Saturday. Seattle. $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 7-11—**University of Washington School of Medicine's Eastern Circuit Course.** Moscow, Id., 7; Walla Walla, Wash., 8; Tri-Cities, Wash., 9; Yakima, Wash., 10; Wenatchee, Wash., 11. $20. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

October 24-25—**Office Management of Chronic Pain.** Seattle. $100. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

AMA 28th Clinical Convention 27
Bank of America ..... 4th Cover
Breon Laboratories Inc.
Bronkotabs 12
Books Received 37
Classified 24, 30
Compton Foundation 30
Dairy Council of California
Medical 13
Dorsey Laboratories
Triaminic Syrup 11
Triaminic Expectorant with Codeine 31
Grubb & Ellis Co. 37
Lakeside Laboratories, Inc.
Norpramin 46, 47
Eli Lilly and Company, Inc.
Manufacturer of Darvon Compound-65 and Darvocet-N 100 26
Loma Linda Foods
Soyalac 7
Asociacion de Medicos Mexicanos, A.C.
Hotel-Club Venture in Mazatlan 49
Mead Johnson Laboratories
Vasodilan 6
Merck Sharp & Dohme
Triavil 20, 21, 22
Aldomet 34, 35, 36
Obetrol Pharmaceuticals
Obetrol 25
Pharmaceutical Manufacturers Association
Prescription Ads 32, 33
Presto Food Products Inc.
Mocha Mix 19
A. H. Robins Company
Allbee with C/Donnotal 17, 18
Roche Laboratories
Bactrim 8, 9, 10
Etudex 14, 15
Dalmane 38, 39
Valium ..... 2nd Cover and Page 1
Roerig (Pfizer)
Emete-Con 4, 5
G. D. Searle & Co.
Pro-Banthine ..... 54 and 3rd Cover
Security Pacific Bank 3, 16
State Compensation Insurance Fund 23
Warner-Chilcott Laboratories
Proloid 42, 43
Wyeth Laboratories
Bicillin/Wycillin 28, 29

November 7-9—**Advances in Internal Medicine.** Thursday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 16 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext 470.

November 14-15—**Drug Therapy.** Thursday-Friday. Fee not set. Contact: Mr. Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 15-16—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. No fee. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext 470.

November 21-22—**Workshop for the Critically Ill Patient.** Thursday-Friday. Olympic Hotel and Harborview Medical Center, Seattle. Contact: Mr. Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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give pain killers?...prescribe frequent eating?...use antacids only

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*Fordtran, J. S., and Collyns, J. A. H.: Antacid Pharmacology in Duodenal Ulcer: Effect of Antacids on Postcibal Gastric Acidity and Peptic Activity, New England J. Med. 274:921-927 (April 28) 1966.

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VOLUME 121 • NUMBER 4 **OCTOBER 1974**

265 *Saving Amputated Digits—Current Status of Replantation of Fingers and Hands*
GARY K. FRYKMAN, MD, and VIRCHEL E. WOOD, MD

270 *Correction of Rectal Prolapse by Anterior Resection*
CARY L. CONYERS, MD, and P. KENT CULLEN, JR., MD

274 *Cardiac Valve Replacement—The Rationale for Earlier Operation*
JOSEPH S. CAREY, MD, WILLIAM G. PLESTED, MD, and CALVIN SCOTT, BS

PEDIATRIC ROUNDS
281 *Myelomeningocele—A Symposium*
Participants: ELMER E. SPECHT, MD, ERNEST K. GOODNER, MD, EMIL A. TANAGHO, MD, MCh, BARBARA PRINCE, MSW, BYRON C. PEVEHOUSE, MD, and PETER COHEN, MD
From the Spina Bifida Group, University of California, San Francisco

MEDICAL STAFF CONFERENCE
305 *Heat Stroke* Discussion by FLOYD C. RECTOR, JR., MD

313 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*General and Family Practice*

319 EDITORIALS • *Cardiac Valve Replacement—The Rationale for Earlier Operation* • *WAMI* • *Myelomeningocele* • *National Health Insurance—An Opportunity for a New Approach*

CASE REPORT
324 *An Anatomical Basis for Unilateral Leg Edema in Adolescent Girls* MAHLON C. CONNETT, MD

327 LETTERS TO THE EDITOR

TRAUMA ROUNDS
329 *Management of Liver Trauma* Chief Discussant: WALTER BALLINGER, MD

MEDICAL EDUCATION
333 *WAMI—An Experiment in Regional Medical Education* M. ROY SCHWARZ, MD

PROGRESS IN PUBLIC ACCOUNTABILITY
342 *Quality of Care and Utilization Assessment—The Hospital Response to PSRO*
WOODBURY PERKINS, MD

NOTES FROM IMPORTANT OR UNUSUAL MEETINGS
349 *International Health—Report of the 27th World Health Assembly of WHO*
FRANCIS W. PARNELL, MD

350 *Conference on the Pathophysiology of Diabetes Mellitus*
DONALD E. McMILLAN, MD, and PETER AMACHER, PhD

356 *In Memoriam*

357 *Annual Meeting of the California Medical Association*

358 *Proposed Amendments to the CMA Constitution*

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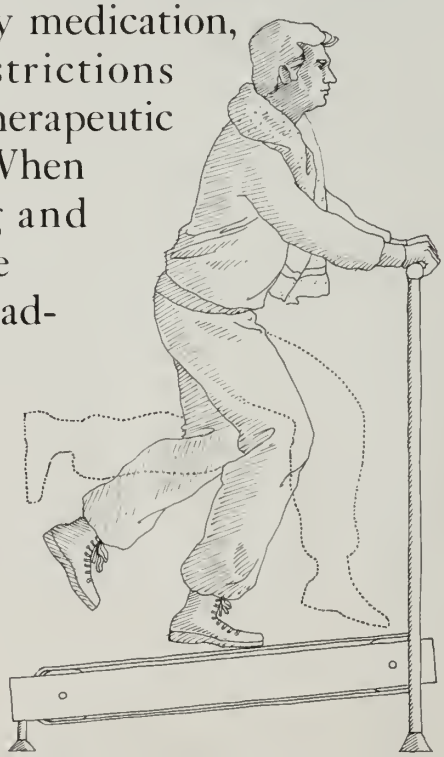

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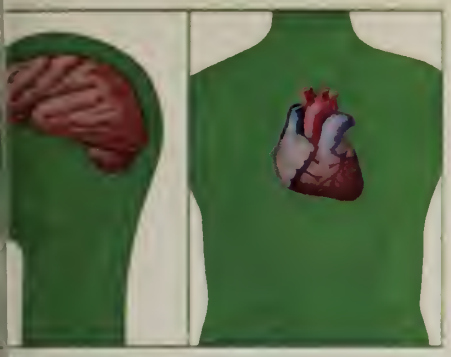

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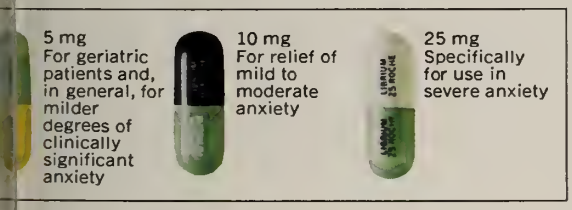

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Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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The Role of the Detail Man

Opinion & Dialogue

Dr. Willard Gobbell
Family Physician
Encino, California

"I may be prejudiced, but I ar very much in favor of the detail me I meet. Most of them are knowledg able about the drugs they promote and can be a great help in acquain ing me with new medication."

Family Physician's Perception

I think that most general practitioners in this area feel as I do about the detail man. Over the years I have gotten to know most o the men who visit me regularly anc they in turn have become aware of my particular interests and the na ture of my practice. They, therefore, limit their discussion as muc as possible to the areas of interest to me. Since I usually see the sam representative again in future visits, it is in his best interest to supply me with the most honest, factual, as well as up-to-date information about his products.

Dr. Jeremiah Stamler
Chairman
Department of Community Health and Preventive Medicine, and Dingman Professor of Cardiology
Northwestern University Medical School

"In the total picture of dealir with health problems in this coun there is a potential for detail men to play a meaningful role."

The Positive Influence

My contact with representatives and salesmen of the pharmaceutical industry is the type of con tact that people in a medical cent research people, and academic people have and that's in all likeli on a somewhat different level fron that of the practicing physician.

Let me touch on how I perso ally perceive the role of the sales representative. These men reach large numbers of health professionals. Thus they could be—and at times actually are—dissemina tors of useful information. They could consistently serve a real ed cational function in their ability t discuss their products.

At present they do distribut printed material, brochures and pamphlets—some of it scientific ally sound and therefore truly use ful—as well as some excellent fil produced by the pharmaceutical industry. When they function in t

He a Source of Information?

Yes, with certain reservations. e average sales representative s a great fund of information out the drug products he is re- onsible for. He is usually able to swer most questions fully and elligently. He can also supply rints of articles that contain a at deal of information. Here, , I exercise some caution. I usu- / accept most of the statements d opinions that I find in the ers and studies which come m the larger teaching facilities. oes without saying that a physi- n should also rely on other rces for his information on armacology.

ining of Sales Representatives

Ideally, a candidate for the sition as a sales representative pharmaceutical company uld be a graduate pharmacist has a questioning mind. I don't k this is possible in every case, so it becomes the responsibility of the pharmaceutical company to train these individuals comprehensively. It is of very great importance that the detail man's knowledge of the product he represents be constantly reviewed as well as updated. This phase of the sales representative's education should be a major responsibility of the medical department of the pharmaceutical company.

I am certain that most of these companies take special care to give their detail men a great deal of information about the products they produce—information about indications, contraindications, side effects and precautions. Yet, although most of the detail men are well informed, some, unfortunately, are not. It might be helpful if sales representatives were reassessed every few years to determine whether or not they are able to fulfill their important function. Incidentally, I feel the same way about periodic assessments of everyone in the health care field, whether they be general practitioners, surgeons or salesmen.

Value of Sampling

I personally am in favor of limited sampling. I do not use sampling in order to perform clinical testing of a drug. I feel that drug testing should rightly be left to the pharmacology researcher and to the large teaching institutions where such testing can be done in a controlled environment.

I do not use samples as a "starter dose" for my patients. I do, however, find samples of drugs to be of value in that they permit me to see what the particular medication looks like. I get to see the various forms of the particular medication at first hand, and if it is in a liquid form I take the time to taste it. In that way I am able to give my patients more complete information about the particular medications that I prescribe for them.

---

acity they are indeed useful; ticularly in the fact that they seminate broadly based educa- al material and serve not just "pushers" of their drugs.

Other Side of the Coin

Obviously, the pharmaceuti- companies are not producing all material as a labor of love— / are in the business of selling ducts for profit. In this regard ambitious and improperly moti- d sales representative can rt a negative influence on the cticing physician, both by pre- ting a one-sided picture of his duct, and by encouraging the ctitioner to depend too heavily drugs for his total therapy. In se ways, the salesman has often orted objective reality and ermined his potential role as an cator.

Industry Responsibility

Since the detail man must be information resource as well as presentative of his particular rmaceutical company, he uld be carefully selected and thoroughly trained. That training, perforce, must be an ongoing one. There must be a continuing battle within and with the pharmaceutical industry for high quality not only in the selection and training of its sales representatives, but also in the development of all of its promotional and educational material.

The industry must be ready to accept constructive as well as corrective criticism from experts in the field and consumer spokesmen, and be willing to accept independent peer review. The better educated and prepared the salesman is, the more medically accurate his materials, the better off the pharmaceutical industry, health professionals and the public—*i.e.*, the patients—will be.

Physician Responsibility

The practicing physician is in constant need of up-dated information on therapeutics, including drugs. He should and does make use of drug information and answers to specific questions supplied by the pharmaceutical representative. However, that information must not be his main source of continuing education. The practitioner must keep up with what is current by making use of scientific journals, refresher courses, and information received at scientific meetings.

The practicing physician not only has the right, but has the responsibility to demand that the pharmaceutical company and its representatives supply a high level of valid and useful information. I feel certain that if such a high level is demanded by the physician as well as the public, this demand will be met by an alert and concerned pharmaceutical industry.

From my experience, my impression is that sectors of the pharmaceutical industry are indeed ethical. I challenge the industry as a whole to live up to that word in its finest sense.

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Subscription prices, $8 ($9 for foreign countries); student subscription $4; single copies 80 cents.

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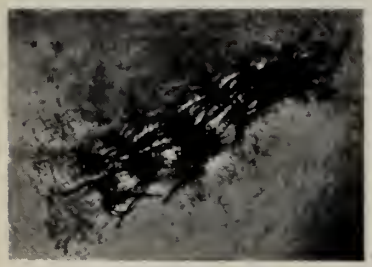
When parenteral analgesia is no longer required, Empirin Compound with Codeine usually provides the relief needed.

HERE Sutures



Empirin Compound with Codeine is effective for visceral as well as soft tissue pain—provides an antitussive bonus in addition to its prompt, predictable analgesia.

(III) **prescribing convenience:** up to 5 refills in 6 months, at your discretion (unless restricted by state law); by telephone order in many states.

Empirin Compound with Codeine **No. 3,** codeine phosphate* 32.4 mg. (gr. ½); **No. 4,** codeine phosphate* 64.8 mg. (gr. 1). *Warning—may be habit-forming. Each tablet also contains: aspirin gr. 3½, phenacetin gr. 2½, caffeine gr. ½.

Wellcome | **Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

fore prescribing, see complete prescribing ormation in SK&F literature or *PDR*. The lowing is a brief summary.

lications: Edema associated with congestive irt failure, cirrhosis of the liver, the nephrotic idrome; steroid-induced and idiopathic ema; edema resistant to other diuretic therapy. o, mild to moderate hypertension.

ntraindications: Pre-existing elevated serum assium. Hypersensitivity to either component. Continued use in progressive renal or patic dysfunction or developing hyperkalemia.

rnings: Do not use dietary potassium supplents or potassium salts unless hypokalemia velops or dietary potassium intake is markedly paired. Enteric-coated potassium salts may ise small bowel stenosis with or without eration. Hyperkalemia (>5.4 mEq/L) has en reported in 4% of patients under 60 years, 12% of patients over 60 years, and in less n 8% of patients overall. Rarely, cases have en associated with cardiac irregularities. cordingly, check serum potassium during rapy, particularly in patients with suspected confirmed renal insufficiency (e.g., elderly or betics). If hyperkalemia develops, substitute iazide alone. If spironolactone is used comitantly with 'Dyazide', check serum assium frequently—both can cause potassiumention and sometimes hyperkalemia. Two aths have been reported in patients on such mbined therapy (in one, recommended age was exceeded; in the other, serum electytes were not properly monitored). Observe ients on 'Dyazide' regularly for possible od dyscrasias, liver damage or other idiocratic reactions. Blood dyscrasias have been orted in patients receiving Dyrenium (amterene, SK&F). Rarely, leukopenia, ombocytopenia, agranulocytosis, and aplastic mia have been reported with the thiazides. tch for signs of impending coma in acutely irrhotics. Thiazides are reported to cross the cental barrier and appear in breast milk. s may result in fetal or neonatal hyperbilinemia, thrombocytopenia, altered carbohrate metabolism and possibly other adverse ctions that have occurred in the adult. When d during pregnancy or in women who might r children, weigh potential benefits against sible hazards to fetus.

Pcautions: Do periodic serum electrolyte and BN determinations. Do periodic hematologic dies in cirrhotics with splenomegaly. Antiertensive effects may be enhanced in postpathectomy patients. The following may ur: hyperuricemia and gout, reversible ogen retention, descreasing alkali reserve h possible metabolic acidosis, hyperglycemia glycosuria (diabetic insulin requirements y be altered), digitalis intoxication (in okalemia). Use cautiously in surgical ents. Concomitant use with antihypertensive nts may result in an additive hypotensive ct.

Averse Reactions: Muscle cramps, weakness, iness, headache, dry mouth; anaphylaxis; n, urticaria, photosensitivity, purpura, other matological conditions; nausea and vomiting y indicate electrolyte imbalance), diarrhea, stipation, other gastrointestinal disturces. Rarely, necrotizing vasculitis, paresias, icterus, pancreatitis, and xanthopsia e occurred with thiazides alone.

Splied: Bottles and Single Unit Packages of 10 capsules.

S&F CO.
olina, P.R. 00630
sidiary of
thKline Corporation

KEEP THE HYPERTENSIVE PATIENT ON THERAPY
KEEP THERAPY SIMPLE WITH

DYAZIDE®

Trademark

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

No potassium supplements
No special K^+ rich diets
Just 'Dyazide' once daily or twice daily

Studies have demonstrated that two prime reasons patients drop out of hypertensive therapy are: (1) the patient failed to understand directions, and (2) the regimen was overly complicated.* Dosage is simple with 'Dyazide', easily understood, once or twice daily, depending on response. There's no need to complicate the regimen with potassium supplements or unwieldy potassium-rich diets.

*E.D. Freis: The Modern Management of Hypertension, V.A. Information Bulletin, 11-35.

TO KEEP BLOOD PRESSURE DOWN AND KEEP POTASSIUM LEVELS UP

THE NATURAL WAY

For more than thirty years PREMARIN (Conjugated Estrog Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrog complex in the proportions foun in its natural source. And for mo than thirty years PREMARIN h enjoyed an unparalleled record clinical efficacy and acceptance

PREMARIN. The only estroge preparation available that conta natural estrogens exclusively and meets all U.S.P. specifications fo conjugated estrogens. Assurance quality for you and your patient

PREMARIN . . . naturally.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN®
(Conjugated Estrogens Tablets, U.S.P.)

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

PREMARIN®

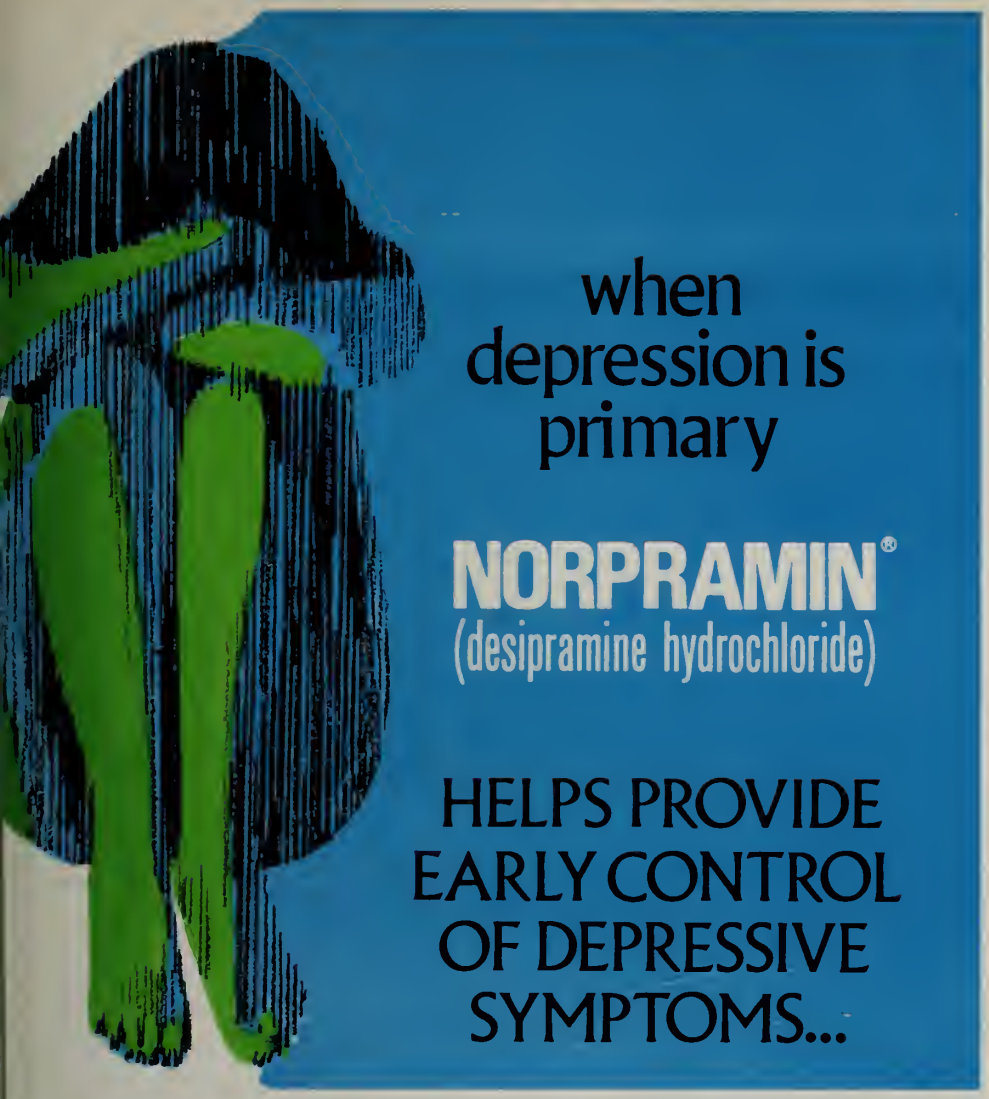
BRAND OF **CONJUGATED ESTROGENS TABLETS, U.S.P.**

CONTAINS ONLY NATURAL ESTROGENS ...NO SYNTHETICS OR SUPPLEMENTS

Ayerst.

AYERST LABORATORIES
New York, N.Y. 10017

When you see anxiety-look for depression
NORPRAMIN®
(desipramine hydrochloride)



Anxiety is an invidious symptom. It feeds upon sickness, gnaws, grows and invades every cranny of psychic pathology adding intensity to torment. Anxiety as a symptom secondary to depression may be so dominant that it obscures the primary diagnosis. It may suggest treatment with tranquilizers which often help. But as the vampire of legend had to have a laurel stake driven through its heart to truly die, so anxiety secondary to depression will not cease to nibble and bite until an antidepressant eradicates the primary illness—and symptomatic anxiety starves.

IN BRIEF:

Indications: Norpramin® (desipramine hydrochloride) is indicated for the relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contraindications: Desipramine hydrochloride should not be given within two weeks of treatment with a monoamine oxidase inhibitor. Contraindications include the acute recovery period following myocardial infarction and hypersensitivity to the drug. Cross sensitivity with other dibenzazepines is a possibility.

Warnings: 1. Extreme caution should be used in patients: (a) with cardiovascular disease, (b) with a history of urinary retention or glaucoma, (c) with thyroid disease or those on thyroid medication, (d) with a history of seizure disorder. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. *Use in Pregnancy:* Safe use during pregnancy and lactation has not been established. 4. *Use in Children:* Norpramin® (desipramine hydrochloride) is not recommended for use in children. 5. This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Therefore, the patient should be cautioned accordingly.

Precautions: This drug should be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with drugs of this class. If possible, dispense in child-resistant containers. It should be kept out of reach of children. Reduce dosage, or alter treatment, if serious adverse effects occur. Norpramin® (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates and may cause exacerbation of phychosis in schizophrenic patients. Use cautiously with anticholinergic or sympethomimetic drugs. Response to alcoholic beverages may be exaggerated. In the concurrent administration of ECT and antidepressant drugs one should consider the possibility of increased risk relative to benefits. Discontinue as soon as possible prior to elective surgery because of possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is neutropenia.

Adverse Reactions: *Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. *Psychiatric:* confusional states (especially in the elderly), hallucinations, disorientation, delusions; anxiety, agitation; insomnia and nightmares; hypomania; exacerbation of phychosis. *Neurological:* paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, hypotonic bladder. *Allergic:* skin rash, petechiae, urticaria, itching, photosensitization, edema (of face and tongue or general), drug fever. *Hametologic:* agranulocytosis, eosinophilia, purpure, thrombocytopenia. *Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar teste, abdominal cramps, diarrhea, stomatitis, black tongue. *Endocrine:* gynecomastia; breast enlargement and galectorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels. *Other:* jeundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturie; perotid swalling; drowsiness, dizziness, weakness end fetigue, headache; elopecia *Withdrewal Symptoms:* Though not indicative of eddiction, ebrupt cessation after prolonged therapy may produce nausea, headache end maleise.

Dosage and Administration: *The usual adult dose:* 50 mg. three times daily; increase if necessary after 7 to 10 days to maximum of 200 mg. daily. Dosages above 200 mg. per day ere not recommended. *Meintenance:* At a lower dose adequate to maintein remission. *Adolescent and gerietric patient dose:* 25 to 50 mg. daily if necessary.

Ovardosage: There is no specific entidote for desipramine, nor are there specific phenomene of diegnostic value characterizing poisoning by the drug. The principles of manegement of coma and shock by meens of the mechenicel respirator, cardiac pacemaker, monitoring of central venous pressure and regulation of fluid- and acid-base balence are well known in most medicel centers. If heart failure is imminent, digitalize promptly.

Manufactured by LAKESIDE LABORATORIES
Division of Colgate-Palmolive Company

Distributed by
LAKESIDE LABORATORIES, INC.
Milwaukee Wisconsin 53201

Part of a series on the clinical, bacteriological and pharmacological aspects of Bactrim therapy.

This is Bactrim against E. coli, Proteus

These are results from clinical trials* in which patients with chroni urinary tract infections (primarily cystitis, pyelitis and pyelonephritis), more than half with obstructive complications, were treated with Bactr for 10 days and evaluated at intervals up to 32 days after termination of therapy. Patients were considered to have a significant bacteriologic response when the urine culture revealed 10,000 or fewer colonies/ml of any single organism cultured from a midstream clean-catch specime

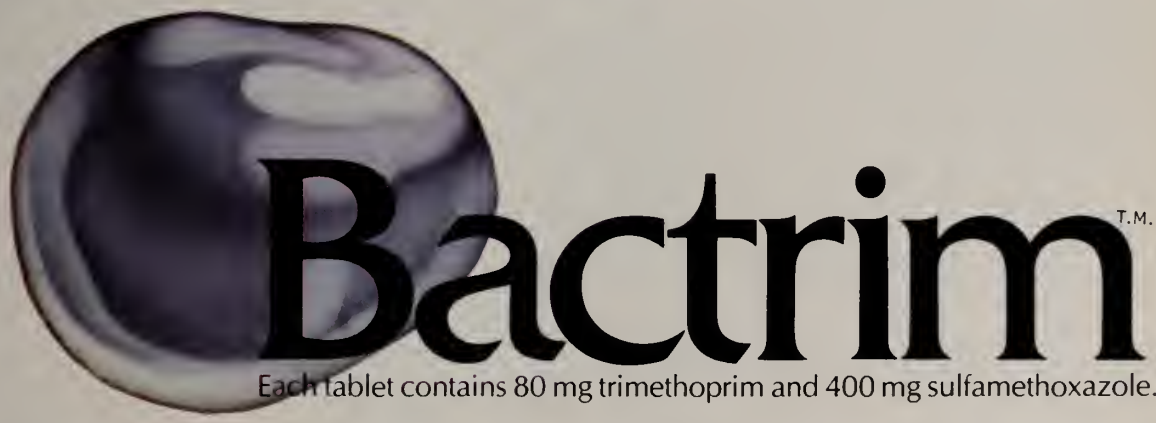
Before prescribing Bactrim, please consult complete product informati for all adverse reactions, contraindications, precautions and warnings.

ROCHE

performance
spp. and Klebsiella

	Excellent initial response* after 10 days of therapy	Impressive response maintained 32 days after termination of therapy
E. coli infections	97.1% of 105 patients	73.1% of 93 patients
Proteus spp. infections	81.1% of 37 patients	60.0% of 35 patients
Klebsiella infections	85.7% of 21 patients	65.0% of 20 patients

*Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley, New Jersey



Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

In cystitis, pyelonephritis and pyelitis diagnosed as chronic and due to susceptible urinary tract pathogens, usually E. coli, Klebsiella-Enterobacter and Proteus mirabilis.

Please see following page for summary of product information.

In cases of cystitis, pyelonephritis and pyelitis diagnosed as chronic*

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

- aggressive antibacterial activity
- interrupts essential metabolic process of susceptible organisms, usually E. coli, Klebsiella-Enterobacter, P. mirabilis, and, less frequently, indole-positive proteus species
- over 91% initial efficacy in clinical studies of patients with urinary tract infection diagnosed as chronic*
- impressive response even in cases with obstructive complications
- not recommended for children under 12, during pregnancy or the nursing period
- no loading dose; two tablets b.i.d. recommended for 10-14 days

*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species).

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in chronic and recurrent urinary tract infections.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia in elderly patients on diuretics, primarily thiazides. Sore throat, fever, pallor or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. Data are insufficient to recommend use in infants and children under 12.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, allergy or bronchial asthma; and in those with glucose-6-phosphate dehydrogenase deficiency, where hemolysis may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritu exfoliative dermatitis, anaphylactoid reactions, periorbital edem conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, sto matitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, men depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *M cellaneous reactions:* Drug fever, chills, toxic nephrosis with oli guria and anuria, periarteritis nodosa and L.E. phenomenon. Du to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfor mides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agent may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: Two tablets b.i.d. for 10 to 14 days. For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regim
15-30	2 tablets every 24 hou
Below 15	Use not recommende

Supplied: Tablets, each containing 80 mg trimethoprim and 400 sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packag of 100; Prescription Paks of 40, available singly and in trays of 1

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

The new nutritional margarine labels have a message about you.

INFORMATION ON FAT AND CHOLESTEROL CONTENT
IS PROVIDED FOR INDIVIDUALS WHO,
ON THE ADVICE OF A PHYSICIAN,
ARE MODIFYING THEIR TOTAL DIETARY INTAKE
OF FAT AND CHOLESTEROL.

Mandatory nutritional statement on the back of all margarine labels.

Saffola® wants you to get the rest of the message.

MAZOLA

Nutrition Information Per Serving

Serving size	14 grams (about one tablespoon)
Servings per container	32
Calories	100
Protein	0 grams
Carbohydrate	0 grams
Fat	11 grams
*Percent of calories from fat	99%
*Polyunsaturated	3 grams
*Saturated	2 grams
*Cholesterol	0 (0. per 100 grams)
Sodium	120 milligrams (865 mg./100 gm.)

Percentage of U.S. recommended daily allowances (U.S. RDA)

Vitamin A 10%

Contains less than 2 percent of the U.S. RDA of protein, Vitamin C, thiamine, riboflavin, niacin, Calcium, and iron.

*Information on fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

IMPERIAL

Nutrition Information Per Serving

Serving size	14 grams (about one tablespoon)
Servings per container	32 (per pound container)
Calories	100
Protein	0 (not a significant source of protein)
Carbohydrate	0
Fat	11 grams
Percent of calories from fat	over 99%
**Polyunsaturated	3 grams
**Saturated	2 grams
**Cholesterol	0 (0. per 100 grams)

*Percentage of U.S. recommended daily allowances (U.S. RDA)**

Vitamin A 10% Vitamin D 15%

*Contains less than 2 percent of the U.S. RDA of Vitamin C, thiamine, riboflavin, niacin, calcium, and iron.

**Information of fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

SAFFOLA

Nutrition Information Per Serving

Serving size	14 grams (about one tablespoon)
Servings per container	32 (per pound container)
Calories	100
Protein	0
Carbohydrate	0
Fat	11 grams
Percent of calories from fats	100%
Polyunsaturated	5 grams
Saturated	2 grams
Contains no cholesterol	

Information of fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

Percentage of U.S. recommended daily allowances (U.S. RDA)

Vitamin A 10% Vitamin E 15%

Contains less than 2 percent of the U.S. RDA of protein, Vitamin C, thiamine, riboflavin, niacin, calcium, and iron.

With the new nutritional labeling, it's all there in black and white. So you can see for yourself. And so can your patients. It adds up to this: Saffola is higher in polyunsaturates than most other margarines including corn oil. And no other margarine is lower in saturated fats than Saffola. Of course, all our products, including Saffola oil and mayonnaise are made with safflower oil.

But we're not kidding ourselves. We know that even if you advise a fat modified diet, your patients might not switch to Saffola. Not unless it tastes every bit as good or better than the spread, oil or mayonnaise they're now using. That's something else they're going to find out for themselves.

How many of your patients know what calcium is?

But they do know what milk is.

These dairy foods have several nutrients in common. The principal one is bone-building calcium, which also helps control muscle action and aids in clotting of the blood. Because they all contain calcium, protein and riboflavin, these foods are considered a part of the Milk Group in the U.S. Department of Agriculture's Four Food Groups system.

Some physicians counsel patients in terms of scientific nutrients. Which is easier for them to understand—foods or nutrients?

For attractive, color copies of the Four Food Groups guide for your patients, write: Dairy Council of California, Box 28F, Sacramento, CA 95825.

Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

Maybe the patient's self-diagnosis is right. He could have hay fever. But that bright red nasal mucosa, along with the thick discharge and excoriation around the nares, strongly suggests that the main problem is a cold. Hay fever or another form of allergic rhinitis may or may not be an underlying factor.

If a complete history and examination rule out allergic rhinitis, the long-term outlook will be a lot more favorable than his own "diagnosis" would have indicated.

But right now, whether he's got allergic rhinitis or a cold, he's suffering from the same irritating symptoms of drip, congestion and stuffiness. Try DIMETAPP EXTENTABS®. They're formulated to relieve these symptoms without much chance of causing drowsiness or overstimulation. Your patients will appreciate the 24-hour relief they can get from just one tablet every 12 hours.

Cold or

Allergy?

Whether it's a cold or an allergy, Dimetapp Extentabs® effectively relieve stuffiness, drip and congestion.

Dimetapp Extentabs®

Dimetane® (brompheniramine maleate), 12 mg.; phenylephrine HCl, 15 mg.; phenylpropanolamine HCl, 15 mg.

A·H·ROBINS

A. H. Robins Company, Richmond, Va. 23220

when pain goes on... and on... and on–

For the patient with a terminal illness, PAIN past, present, and future can dominate his thoughts until it becomes almost an obsession. The more he is aware of the pain he is now experiencing, the more difficult it is to erase his memory of yesterday's pain, and to allay his fearful anticipation of tomorrow's pain.

Surely the last thing this patient needs is an analgesic containing caffeine to stimulate the senses and heighten pain awareness. A far more logical choice is Phenaphen with Codeine. The sensible formula provides ¼ grain of phenobarbital to take the nervous "edge" off, so the rest of the formula can help control the pain more effectively. Don't you agree, Doctor, that psychic distress is an important factor in most of your terminal and long-term convalescent patients?

the analgesic formula that calms instead of caffeinates

Phenaphen® with Codeine

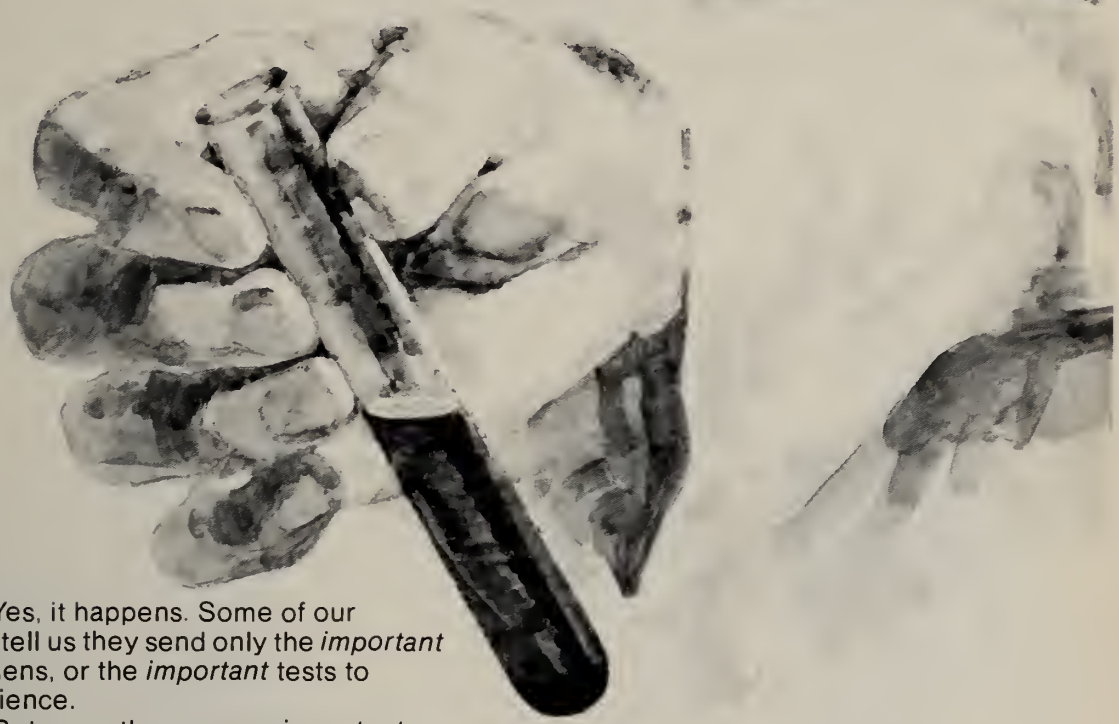
Phenaphen with Codeine No. 2, 3, or 4 contains: Phenobarbital (¼ gr.), 16.2 mg. (warning: may be habit forming); Aspirin (2½ gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Codeine phosphate, ¼ gr. (No. 2), ½ gr. (No. 3) or 1 gr. (No. 4) (warning: may be habit forming).

Indications: Provides relief in severer grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products, excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** Phenaphen No. 2 and No. 3—1 or 2 capsules every 3 to 4 hours as needed; Phenaphen No. 4—1 capsule every 3 to 4 hours as needed. For further details see product literature.

(III) Phenaphen with Codeine is now classified in Schedule III, Controlled Substances Act of 1970. Available on written or oral prescription and may be refilled 5 times within 6 months, unless restricted by state law.

A. H. Robins Company, Richmond, Va. A·H·ROBINS

"Send it out to Bio-Science. It's important."



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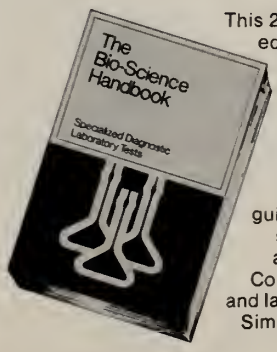

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to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

"...and she'd jump every time the phone rang."

"All right, I agree, she was obviously very anxious...you said she hadn't been sleeping...."

"She felt *tired enough* to sleep... not relaxed enough...food, too... she's too nervous to eat...says she *can't* relax...afraid there's something very wrong with her."

"...that's a good place t Did you find anything w with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

MSD MERCK SHARP DOHME

For a brief summary of prescribing information, please turn to the following page.

ca thing... negative... nothing
nically wrong. Still has a
ist of somatic complaints.
ried to reassure her... to let
alk... to help her sort things
She's been in to see me a
ber of times."

"...what about medication?"

"Just what I was coming to...
I've had her on tranquilizers.
And *that's* what puzzles me. I'm
not getting the response I hoped
for. She's no better... perhaps a
little worse. It's sad to see."

"...I think *'sad'* may be what
you're not seeing! You know,
this sounds like another case
where the *anxiety* is so clear and
pervasive we tend to overlook
the depressive part of the picture.
I'm not sure that we shouldn't
almost always think of anxiety
with depression... not anxiety
alone. Take another look at your
records... talk to her some more.
If you decide she's depressed,
I think you might want to
consider TRIAVIL.... It can help
relieve her entire symptom
complex... control the anxiety...
while at the same time treat
the depression."

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

to help treat what you often find: obvious moderate to severe anxiety with a less obvious underlying depression

Available:
TRIAVIL® 2-25: Each tablet contains
2 mg. perphenazine and 25 mg. amitriptyline HCl

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2 mg. perphenazine and 10 mg. amitriptyline HCl

TRIAVIL® 4-25: Each tablet contains
4 mg. perphenazine and 25 mg. amitriptyline HCl

TRIAVIL® 4-10: Each tablet contains
4 mg. perphenazine and 10 mg. amitriptyline HCl

INITIAL THERAPY FOR MANY PATIENTS
TRIAVIL® 2-25 (or TRIAVIL® 4-25) t.i.d. or q.i.d.

FOR FLEXIBILITY IN ADJUSTING MAINTENANCE THERAPY
TRIAVIL® 2-10 (or TRIAVIL® 4-10)

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either constituent alone.

Perphenazine: Side effects may be any of those reported phenothiazine drugs: extrapyramidal symptoms (opisthotonus, logyric crisis, hyperreflexia, dystonia, akathisia, acute dyskir ataxia, parkinsonism) can usually be controlled by the concon use of effective antiparkinsonian drugs and/or by reduction in age, but sometimes persist after discontinuation of the phenothia

Tardive dyskinesia may appear in some patients on long-term apy or may occur after drug therapy with phenothiazines and re agents has been discontinued. The risk appears to be greater derly patients on high-dose therapy, especially females. Symp are persistent and in some patients appear to be irreversible syndrome is characterized by rhythmical involuntary movemer the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffi cheeks, puckering of mouth, chewing movements). Involuntary r ments of the extremities sometimes occur. There is no known ment for tardive dyskinesia, antiparkinsonism agents usually d alleviate the symptoms. It is advised that all antipsychotic agen discontinued if the above symptoms appear. If treatment is rein ted, or dosage of the particular drug increased, or another drug stituted, the syndrome may be masked. It has been suggested fine vermicular movements of the tongue may be an early sign c syndrome, and that the full-blown syndrome may not develop if cation is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itc erythema, urticaria, eczema, up to exfoliative dermatitis); oth lergic reactions (asthma, laryngeal edema, angioneurotic ec anaphylactoid reactions); peripheral edema; reversed epinep effect; hyperglycemia; endocrine disturbances (lactation, g torrhea, gynecomastia, disturbances of menstrual cycle); al cerebrospinal fluid proteins; paradoxical excitement; hyperte hypotension, tachycardia, and ECG abnormalities (quinidine-li fect); reactivation of psychotic processes; catatonic-like state tonomic reactions, such as dry mouth or salivation, head anorexia, nausea, vomiting, constipation, obstipation, ur frequency or incontinence, blurred vision, nasal congestion, a change in pulse rate; hypnotic effects; pigmentary retinopathy neal and lenticular pigmentation; occasional lassitude, muscle ness, mild insomnia. Other adverse reactions reported with va phenothiazine compounds include blood dyscrasias (pancyto thrombocytopenic purpura, leukopenia, agranulocytosis, eosi lia); liver damage (jaundice, biliary stasis); grand mal convuls cerebral edema; polyphagia; photophobia; skin pigmentation failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not report this drug, but which have occurred with other pharmacologicall lar tricyclic antidepressant drugs. *Cardiovascular* Hypotensio pertension; tachycardia; palpitation; myocardial infarc arrhythmias; heart block; stroke. *CNS and Neuromuscular* fusional states; disturbed concentration; disorientation; delus hallucinations; excitement; anxiety; restlessness; insomnia, mares; numbness, tingling, and paresthesias of the extrem peripheral neuropathy; incoordination; ataxia; tremors, seizures ation in EEG patterns; extrapyramidal symptoms; tinnitus *ticholinergic:* Dry mouth; blurred vision; disturbanc accommodation; constipation; paralytic ileus; urinary retention; tion of urinary tract. *Allergic:* Skin rash; urticaria; photosensitiz edema of face and tongue. *Hematologic:* Bone marrow depre including agranulocytosis; leukopenia; eosinophilia; purpura; bocytopenia. *Gastrointestinal:* Nausea; epigastic distress; von anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; tongue. *Endocrine:* Testicular swelling and gynecomastia in the breast enlargement and galactorrhea in the female; increas decreased libido; elevated or lowered blood sugar levels. *Othe* ziness, weakness; fatigue; headache; weight gain or loss; incre perspiration; urinary frequency; mydriasis; drowsiness; jaundic pecia. *Withdrawal Symptoms:* Abrupt cessation after prolonge ministration may produce nausea, headache, and malaise. The not indicative of addiction.

OVERDOSAGE: Treatment is symptomatic and supportive. Ho the intravenous administration of 1-3 mg of physostigmine sali has been reported to reverse the symptoms of amitriptyline p ing. On this basis, in severe overdosage with perphenazin triptyline combinations, symptomatic treatment of ce anticholinergic effects with physostigmine salicylate should b sidered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

MS
MER
SHA
DOH

Case history #4

Charles' well-being comes first.

Charles' being well comes first.

In September 1968, while working as a driver/salesman for a Sacramento beverage ompany, Charles Foster's automobile overturned. He was thrown from the car and sustained number of serious injuries, including a compression fracture of the vertebrae with cord njury, making him paraplegic.

During Charles' initial period of intensive care, State Fund cooperated with his doc- ors, setting up a long-range program of health care. Charles suffered a cardiac arrest during pinal surgery, but he was successfully resuscitated and continued to improve. After leaving ne hospital, he entered the Kaiser Foundation Rehabilitation Center in Vallejo, where he uickly learned to adapt to his paralysis.

State Fund's rehabilitation staff visited Charles regularly to help him plan his new fe. They helped him buy a specially equipped car to drive to and from school and arranged nd paid for home alterations to accommodate his wheelchair and his impairment.

In 1973, Charles Foster took advantage of State Fund's *Therapeutic Capitalization* rogram, enabling him to receive a lump-sum payment for the total projected cost of his life- me medical and living expenses, which he invested in secure mutual funds and in a busi- ess of his own. Today, Charles is teamed with another paraplegic, and together they operate he Wheelchair Boutique, specializing in sales, repair, and rental of hospital equipment.

Charles has come a long way since his accident, with courage and determination— nd the help of State Fund.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND

IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticana; serum sickness-like reactions including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. polyvinylpyrrolidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
NJECTION
Bicillin® LONG-ACTING
STERILE BENZATHINE PENICILLIN G (SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

Kids' Stuff

Triaminic Syrup
the orange medicine from Dorsey

Dorsey
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If we had managed Scarlett O'Hara's account, Tara might not have gone with the wind.

Not everyone can be a skilled money manager. When such a person is left with the task of managing an estate, the results can be rather sad.

Security Pacific Bank's Testamentary Trust Service assures that your assets will be managed with the skill and experience of one of the country's leading financial institutions. Those assets are invested according to your family's individual economic needs, and the trust can be flexible enough to change with those needs.

A Security Pacific Bank Testamentary Trust can also reduce probate costs and unnecessary expenses. Example:

A man leaves an estate of $300,000 outright to his wife. And she passes it on to the children. The money will be taxed a total of $88,000. If his estate were left in trust for his wife, there could be a saving of as much as $58,000.

Then there's the human element. The presence of a Trust Officer who takes a sincere interest in the beneficiaries he serves. You can meet this person by calling any of our over 470 branches for an appointment. There is no cost or obligation.

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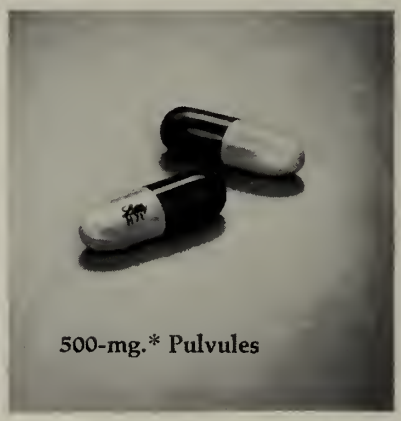
it makes sense

250-mg.* Pulvules®



500-mg.* Pulvules

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250 mg.*/5 ml.
100-ml. size

125 mg.*/5 ml.
60 and 100-ml.
sizes

Pediatric Drops

100 mg.*/ml.
10-ml. size

*Equivalent to cephalexin.

Additional information available to the profession on request.

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THE WESTERN
Journal of Medicine

Refer to: Frykman GK, Wood VE: Saving amputated digits—Current status of replantation of fingers and hands. West J Med 121:265-269, Oct 1974

Saving Amputated Digits

Current Status of Replantation of Fingers and Hands

GARY K. FRYKMAN, MD, *and* VIRCHEL E. WOOD, MD, *Loma Linda, California*

Since the advent of microsurgery in the 1960's it has become possible to sucessfully repair vessels as small as 0.5 mm in diameter, which makes the replantation of totally severed digits possible. Some centers have reported 50 to 60 percent survival of completely severed digits and up to 100 percent survival of amputated hands and of partially amputed but otherwise non-viable digits that were reattached. In view of this success, severed members should be considered as potentially replantable.

The recommended indications for replantation are: (1) multiple digital amputations at or proximal to the proximal interphalangeal joint; (2) amputation of the thumb; (3) amputation of the wrist or hand; (4) partially attached digits that are non-viable without reattachment.

The surviving replanted digits give functional improvement to the hand and prove cosmetically acceptable.

THE TIME IS PAST when all amputated parts must be considered irrevocably lost. Relatively clean amputated parts should be considered potentially viable. With the advent of microvascular techniques, small vessels can be anastomosed, making possible restoration of viability and function. No prosthetic device, lacking as it does the sense of touch, can ever adequately substitute for an amputated part.

The replantation era began in 1962 when Malt[1] performed the first successful replantation of an arm, in a 12-year-old boy. This report was followed by other successful attempts at upper extremity replantations.[2-5] Survival and function of replanted legs and feet have been reported from China.[6]

Although technically more difficult to perform, the replantation of hands and fingers gives better functional results than replantation where amputation occurred at more proximal levels.[7,8]

Unfortunately the potential for replantations distal to the wrist has not received much attention in the general literature. It is hoped that this review will stimulate such interest by discussing the development of replantation operations, indications for the procedure, current techniques and, finally, functional results.

Development of Replantation Surgery

In the first decade of this century Carrel and Guthrie[9] showed that vessels can be successfully sutured. However, during the next 30 years little progress was made. Ligation of injured arteries

From the University Hand Service and the Department of Orthopedic Surgery and Rehabilitation, Loma Linda University School of Medicine.

Submitted April 26, 1974.

Reprint requests to: G. K. Frykman, MD, Department of Orthopedic Surgery and Rehabilitation, Loma Linda University Medical Center, Loma Linda, CA 92354.

was the standard practice during World War II and amputation was required in 49 percent of such cases. It was not until the Korean War period that primary vascular reconstruction was routinely practiced, and the amputation rate was only 13 percent.[10] It was not possible to successfully repair vessels smaller than 4 mm until the development of microvascular surgical technique.

Jacobson and Suarez,[11] in 1960, pioneered the use of the microscope for vascular repairs, and this, along with the use of microinstruments and specialized suture material, made possible successful repairs of vessels as small as 0.5 mm in diameter.

Replantation operations in animals was begun in 1954 by Lapchinsky[12] of Russia, who gained some renown with his limb replantation studies of dogs. Eiken,[13] in research on replanted dogs' legs, found that serious muscle necrosis resulted if ischemia exceeded 6 hours. In 1963, Ch'en Chung-Wei of Shanghai[14] began experimental replantation of rabbit ears by microvascular anastomosis. Buncke[15] performed replantation of primate digits in 1964.

In 1964 the first successful hand replantation was reported by Horn,[16] a British surgeon working in China. In 1962, Kleinert and Kasdan[17] first successfully replanted a partially amputated nonviable thumb that was left attached by only a dorsal skin bridge. The digit survived following successful digital arterial repair. Others have subsequently recorded up to 100 percent success with digital replantation of partially amputated digits.[18-20] The first successful replantation of a completely cut off digit was performed in Peking in 1964.[6] However, the first report of a successful thumb replantation was by Komatsu and Tamai[21] in 1968. Following these reports there were only isolated successes with replanted digits until recently when O'Brien[18] reported 21 cases of digital replantation, Tamai[22] 4 cases, Tsuge[23] 12 cases, and Ch'en[14] 231 cases.

Development in microscopes has been mainly refinements that permit a surgeon to change magnification and focus with foot pedals and so give adequate magnification view for one or two assistants.

A major problem that is still incompletely solved is that of thrombosis of the tiny vessels after they have been repaired. The development of smaller suture which has decreased the amount of foreign body in the wound has helped considerably. Although suture as small as 10 microns in diameter has been developed,[15] most microvascular repairs are now done with suture in the 18 to 22 micron range (10-0 nylon) swaged on a 3 mm curved, tapered needle.[24]

Among the more significant advances in surgical instruments has been the development of microclamps to temporarily occlude the vessels while they are being sutured.[15,25-27]

Anticoagulation, particularly with heparin, increases the survival rate.[28] However, the initial thrombus during blood flow is due to platelet aggregation secondary to platelet contact with collagen at the cut end of the vessel and thus heparinization would not be expected to prevent this platelet thrombus. Local instillation of magnesium sulfate has been shown to prevent platelet thrombus.[29] A variety of pharmacological approaches have been attempted and are under further investigation in our laboratory.

Systemic dipyridamole[18] and local intraoperative instillation of lidocaine, papaverine hydrochloride[28] or chlorpromazine[30] have been used to prevent vascular spasm.

Indications for Replantation

We recommend replantation in cases of relatively clean amputations as follows: for (1) any digit that remains partially attached but is nonviable; (2) multiple digital amputations at or proximal to the proximal interphalangeal joint; (3) amputation of the thumb; (4) amputation of the wrist or hand.

Whether or not to replant a single complete finger is a matter of judgment and depends on the patient's occupation, age, the digit involved and the patient's wishes. The patient's general condition and the presence of other more serious injuries may contraindicate attempting replantation. If the amputated part is moderately or severely crushed, replantation is usually unsuccessful. The same is true of avulsion injuries.

Technique of Replanting Digits

The amputated part of a digit should be wrapped in a sterile sponge that has been soaked in saline solution and placed in a clean (preferably sterile) plastic bag. Preserving solutions, soaps or antibiotic solution should not be used. The bag should be placed in a container of ice to keep the digit cool, but not freezing. If the patient is in shock, his condition should be stabilized and then he should be sent to the nearest replantation center. The shorter the delay before revasculari-

Figure 1.—Hand of patient in case herein reported, with long, ring and little fingers amputated by power sander.

zation the greater the success rate, and in general the upper limit of 8 hours is most desirable for preserving viability of muscle. Amputated digits, may, however, survive longer periods of ischemia, particularly if the amputated part has been cooled rapidly and kept cool.

It is crucial that a replantation team be ready to operate immediately when the patient arrives. In the emergency room, tetanus prophylaxis and intravenous administration of antibiotics should be carried out, and x-rays should be taken of the injury site and the amputated part.

The preferred anesthesia is a long-acting brachial plexus block with supplementary general anesthesia as necessary if the operation is prolonged.

It is helpful to have two teams in the operating room, one to explore and prepare the amputated part and a second to debride and prepare the injured extremity. In preparing the amputated extremity, care must be taken not to damage the vessels. Meticulous debridement is done while digital arteries and veins are searched for. Shortening the bone usually is necessary and this should be done liberally before internal fixation is carried out, so that there will be no tension on the vascular repairs. Heparin is instilled locally in the injured vessels before repair and one unit of low molecular weight dextran is given in the operating room. Two veins for each artery should be repaired under the microscope with interrupted 10-0 nylon. The tourniquet is released once arterial repair is done, and if veins have not been previously found, the bleeding points will help locate them for repair. If time and conditions of the wound permit, the nerves and tendons should be repaired. A non-occlusive dressing is applied.

Postoperatively the hand is elevated just above the level of the heart, and circulation is checked hourly. Heparin and low molecular weight dextran are given. If arterial thrombosis occurs, it will usually be within the first 24 hours; and if it does, the patient should be taken back to the operating room for thrombectomy and a new repair. Venous thrombosis which is sometimes associated with infection occurs three to ten days postoperatively and is the more common cause of replantation failure.[19]

If venous anastomosis cannot be done, postoperative anticoagulation is not used. In this case the wound is left open, and heparin-soaked sponges are applied to the wound and changed frequently.[31]

Sympathetic block may be done to relieve vascular spasm, but should not be done if the patient is anticoagulated.

Report of a Case

The patient was a 50-year-old man whose dominant long, ring and little fingers had been completely amputated by a power sander at the metacarpophalangeal joint level (Figure 1). After debridement, the little finger was found to be the least crushed, so it was sutured to the head of the fourth metacarpal by repair of both digital arteries and three veins. The nerves were primarily repaired, as were the joint capsule and the extensor and the flexor digitorum profundus tendons.

A year later flexor tenolysis was carried out with resultant total active motion in the small finger of 52° (Figure 2). The patient rated motion and sensation satisfactory. He returned to work as a carpenter and found the hand useful for grasping and pinching; and he had protective sensation and no pain in the replanted digit. The overall result was rated fair. Although the replanted digit functioned imperfectly, it became the important third digit in an otherwise two-digit hand.

Results of Digital Replantation

O'Brien[18] reported 13 survivals out of 21 complete digital amputations, a 62 percent survival rate. In 10 incomplete amputations he reported 100 percent survival rate. Tsuge[23] accounts for 12 cases of multiple digital amputations where at least one digit survived in each hand. Ch'en[14] recently reported 231 complete digital amputations with

Figure 2.—A year after attachment of little finger to fourth metacarpal head and one month after tenolysis. Picture at top shows active extension. Lower picture shows effective pinch of attached digit against thumb.

114 replantations surviving, giving a survival rate of 49.4 percent. In the Canton[6] series there were 19 survivals of 29 digital amputations, or 65 percent.

The early functional results of surviving digital replantations are encouraging. However, a long term follow-up on a large number will be needed before final judgment can be made. Visitors to China have reported two-point discrimination of less than 1 cm in total digital replantations.[6] Forty-one percent of the patients in Ch'en's series returned to their former jobs and one patient returned to playing the accordion. O'Brien reported two point discrimination of 3 to 10 mm in replanted digits.

In an attempt to evaluate functional results of a group of digital replantations, we personally interviewed 20 patients with 25 surviving replantations of incomplete digital amputation and two patients with replanted completely severed digits. The replantations were done between 1963 and 1972 with an average postoperative follow-up of 3.7 years.[32] Several subjective and objective criteria were used in evaluating the function of these replanted digits. Only one patient had reported moderate pain, two mild pain, and 24 no pain in the injured digit at follow-up. Two-thirds of the digits were rated by the patients as having satisfactory sensation in every way. Only one felt the digit was cosmetically unattractive.

The principal factors of pain, and limited range of motion, sensation and use were rated to give an over-all functional result. We found 80 percent of the patients with replanted incomplete digital amputations had good or excellent results. The two patients with replanted complete digital amputations showed a fair and a poor result by our criteria. Eighteen of the 20 patients with incomplete digital amputation and the two patients with surviving complete digital reattachment remained in their same job at follow-up, including six of eight who had jobs requiring skilled use of their hands. No patient wanted the digit reamputated, and patients were enthusiastic about their resultant function, even though only 12 digits were rated better than 75 percent of normal function. It appeared that the surviving replanted digits gave functional improvement to the hand in all cases interviewed.

It is recognized that all the surviving digits are not completely functional. However, neither O'Brien nor Ch'en reported any late amputations in their series which totaled 127 survivals. In the authors' series, only two of 52 total surviving digital amputations required late reamputation.

Discussion

It is recognized that not all patients may want replantation. Extra hospitalization is required, and the possibility of nonsurvival is present. In one series,[19] the average worktime lost by patients with surviving replanted digits was seven months, against four months for patients with non-surviving digital amputations The average worktime lost for patients in whom replantation was not attempted was two and a half to three months. For a single finger amputation in a working man, replantation may not be worth the expense and the longer period of disability, even though the permanent disability may be less. Nonetheless,

replantation can be offered to patients as a reasonable alternative to simple closure of the amputation.

Replantation is not an operation for the casual hand surgeon. As more surgeons are trained in microvascular techniques, the replantation will become available to more patients. Entin[33] proposed that a replantation center be established for each two to ten million people. Modern air and ground transportation make most patients close enough to replantation centers to make replantation an option. In this way the patient's interest will be served best, and more amputated parts will be saved.

Clearly replantation is here to stay. The age has passed when one must consider an amputated part irretrievably lost. The very low incidence of reamputation and the high subjective rating of the function of the reattached digits demonstrate patient endorsement of replantation. Since microvascular surgery is still in its infancy, further refinements in technique and more rapid transportation of patients for replantation should improve the survival rate and function of the surviving parts.

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Refer to: Conyers CL, Cullen PK Jr: Correction of rectal prolapse by anterior resection. West J Med 121:270-273, Oct 1974

Correction of Rectal Prolapse by Anterior Resection

CARY L. CONYERS, MD, *and* P. KENT CULLEN, JR., MD, *Santa Barbara*

During the past three consecutive years low anterior resection with rectopexy has been used to correct complete rectal prolapse in nine patients. There have been no recurrences and only two complications, one a presacral abscess not related to anastomotic malfunction, and the other a fecal fistula in an 81-year-old woman, which resolved spontaneously without colostomy.

RECTAL PROLAPSE is an abnormal falling-down of all three layers of the rectum or rectosigmoid colon. Generally, three diagnostic types or classes are recognized. Class I, or mucosal prolapse, involves only a 2 or 3 cm length of protruded surface tissue of the anorectum. This is in all probability a hemorrhoidal prolapse and is not considered a true rectal prolapse. Class II probably represents an early stage of complete prolapse, in which intussusception of some degree of the rectosigmoid has occurred, but without protrusion through the anal orifice. Even though this stage produces symptoms, visual diagnosis is unusual. Class III is a complete protrusion (procidentia) of intussuscepted rectum through the anal canal, with or without a concomitant pouch of Douglas sliding hernia. Rectal prolapse is uncommon, occurs most often in persons between ages 50 and 80, and predominantly affects women. Psychiatric patients in institutions and persons who damage the cauda equina or sacral nerves also have a higher incidence of rectal prolapse. In the sixteenth century, Ambroise Paré[1] described rectal prolapse in just such nerve-damaged patients.

Largely through the work of Moschcowitz[2] in 1912, modern surgeons have operated on the anatomic basis that complete prolapse was primarily a cul-de-sac sliding hernia with the protruding rectum composing the posterior hernial wall. Until recently, then, many surgical procedures[2-5] have attempted mainly to repair an attenuated levator sling and endopelvic fascia, and to obliterate the hernial sac, while giving only secondary attention to the rectum itself. With the introduction of anterior resection as a new surgical treatment for this problem by Stabins[6] in 1951, and the later advocacy of this method by Muir,[1] Bacon,[7] and Beahrs and Hill,[5] a gradual awareness has developed that intussusception and improper alignment of redundant rectosigmoid colon are the initial anatomic defects. The weakened pelvic floor musculature and patulous anal sphincters usually may be considered secondary developments. That at least 50 different procedures exist to correct this problem exposes the quandary created by etiologic uncertainties.[5,7]

From the Department of Surgery, Santa Barbara Cottage Hospital.

Submitted April 29, 1974.

Presented at a meeting of the Southern California Chapter of the American College of Surgeons, January 19, 1974.

Reprint requests to: P. K. Cullen, Jr., MD, 230 W. Pueblo, Santa Barbara, CA 93105.

Figure 1.—The patient was a 53-year-old white man with 12 cm protruded prolapsed rectum, whose "hemorrhoids" had worsened during the preceding six months. The lesion appeared beefy red and was decidedly edematous. Soiling and bleeding were recent complaints.

Figure 2.—Rectal protrusion of 10.5 cm in a 77-year-old white woman. Incontinence had been present for two years and was gradually worsening.

Recent investigations of the physiology of continence and defecation[5,8,9] have given us insight enough to realize that functional as well as anatomic components act to produce the incontinent patient with rectal prolapse. According to Todd,[10] Ripstein,[11] Broden and Snellman,[8] and Nigro,[12] normal mechanisms of defecation require intact neural receptors and pathways, and normoreactive anorectal smooth and striated musculature. The usual patient with rectal prolapse has a depressed, or asynchronous, urge to defecate. A long history of severe chronic straining, poorly developed bowel habits, constipating diets, and regular use of laxatives[9] is often elicited. Thomas[13] postulated a correlation between decreased rectal sensory appreciation and a chronically distended rectum. Ill-timed conscious cortical control of sphincters which repeatedly oppose the involuntary, possibly humorally induced,[14] muscle action of the colorectum surely adds to the complex processes that bring about rectal prolapse. When such an afflicted patient increases his intra-abdominal pressure even slightly by coughing or laughing, for example, the redundant rectum is seen to lose its once normal horizontal position on the sacral hollow and assume a straightened, anterior position. This motion allows easy passage of stool and rectum through patulous anal sphincters. For repair of this condition, a procedure in which low anterior resection and rectopexy removes the redundant rectosigmoid and replaces the rectum into the sacral hollow, has been used with favorable results at the Santa Barbara Cottage Hospital.

Cases and Techniques

Between July 1970 and January 1974, nine patients with complete rectal prolapse were operated upon by one of us (P.K.C.) using low anterior resection and rectopexy. Follow-up by physical examination of all patients in office was completed to January 1974. Three patients were operated upon more than two and a half years ago, three more than one and a half years ago, and three within the year preceding the last date of follow-up. No deaths have occurred to date.

There were eight women and one man. Three were between 21 and 31 years of age, two between 50 and 60, and four between 67 and 81.

Four of the nine patients had had from one to four previous other procedures for the condition, and three of the four had had earlier hemorrhoidectomy by "amputative excision of hemorrhoids." Two had had unsuccessful Altemeier procedures and two had had recurrences after Thiersch wire or Mersilene sling placement around the anal orifice.

The range of lengths of the prolapsed section at the time of operation was 8 to 15 cm (Figures 1 and 2). The duration of prolapse from the time

TABLE 1.—*Collected Results in Operations for Rectal Prolapse (1972)*
(From Theuerkauf, Beahrs, and Hill, adapted and brought up to date)*

	Patients	*Mortality (Percent)*	*Recurrence (Percent)*
Thiersch—Wire anoplasty	114	..	68.0
Delorme—Perineal rectal plication	336	2.4	25.0
Miles-Gabriel—Perineal rectosigmoidectomy	507	0.6	40.8
Altemeier—Perineal rectosigmoidectomy	119	..	6.7
Dunphy—Two-stage perineal-abdominal operation	29	..	3.4
Moschcowitz—Obliteration of cul-de-sac	128	2.3	47.8
Pemberton—Suspension-fixation	250	0.4	18.9
Kummel—Suspension-fixation (alcohol injection)	1,029	1.3	12.4 (7.7)
Graham-Goligher—Repair of pelvic floor	217	2.8	8.0
Orr—Suspension fascia lata slings	62	..	5.0
Nigro—Levator sling	5	..	..
Anterior or sigmoid resection, fixation	202	2.0	3.6
Wells—Ivalon sponge wrap	109	3.7	1.9
Ripstein—Fascia lata/teflon hammock	128	0.8	0.7
Devadhar—Reversed intussusception, plication	28	3.6	..

*Compiled by Steichen.[16]

of first protrusion ranged from 8 months to 21 years. One young woman said she had "always" had the prolapse, and for a long time thought it was a normal condition. Most of the older patients had not noted onset of protrusion until their middle or later years.

Surgical Procedure

All of the patients had a 48-hour preoperative mechanical and antibiotic bowel preparation. Their diet was changed from low residue to clear liquids the day before and cleansing enemas were administered the morning of operation. During the later period of the time covered by this report, antibiotics were given intravenously 12 and 6 hours before operation, and administration was continued during the procedure and for three to five days thereafter.

The dissection procedure used was as described by Mayo.[15] In the procedure as we used it, it is very important to mobilize the rectum all the way down to the tip of the coccyx, as in the Miles' abdominoperineal resection, sacrificing the "lateral rectal stalks" and the middle hemorrhoidal pedicles. An adequate rectal segment, at least 5 cm, is preserved and "fixed" into the presacral hollow with non-absorbable suture material (2-0 silk). The redundant bowel is excised and the anastomosis should be established at a convenient site in the sigmoid or rectosigmoid area rather than deep in the pelvis. This allows adequate anastomosis with minimal risk of leakage or other anastomotic complications. If a definite palpable superior hemorrhoidal vessel can be followed to the distal rectal stump, it and the mesentery are preserved, thus creating a modified mesenteric tube vessel graft to ensure blood supply to the distal stump. This step may be unnecessary but it seems to allow preservation of a longer rectal segment which otherwise could become non-viable after sacrifice of the middle hemorrhoidal pedicles. After obliteration of any existing "cul-de-sac defect," reperitonealization is performed below the site of anastomosis. Drains are usually placed into the sacral hollow and in the vicinity of the fixed anastomotic junction. They are removed as drainage subsides. The patients are given nothing by mouth until bowel activity returns and then are graduated from clear liquids to moderate residue diet on dismissal from the hospital.

Results

No deaths have occurred. There were only two postoperative complications. A fecal fistula manifesting itself on the ninth postoperative day resolved after three weeks of antibiotics and conservative management. The second complication was a presacral abscess occurring on the eighth postoperative day. Since it was determined by roentgenographic contrast study not to be related to malfunction of anastomosis, surgical drainage through the posterior rectal wall below the anastomotic junction was carried out. Fever, diarrhea, and sacral pain cleared after five days of antibiotics and enteric rest.

The average length of hospital stay was 16

days, not including the two complicated cases, in which 38 and 25 hospital days were required.

There were no recurrences, not even mucosal prolapse, as of January 1974. This result is encouraging in view of the fact that recurrences from six months to two years postoperatively are common.[5] Precise assessment of degree of continence is difficult, but all patients have enjoyed improvement of function with no soiling or bleeding since discharge from hospital. Certainly none were made worse. Most are greatly relieved and consider the operation a thorough success. Best results were obtained in patients with the least degree of incontinence and the best sphincter tone preoperatively.

Comments

A review of all existing procedures for rectal prolapse is not the purpose of this paper. However, a table of mortality and recurrence rate associated with various widely used procedures (compiled by Steichen[16]) is included for comparison. (See Table 1.) Anterior resection compares favorably with other operations in most respects.[5,16] This procedure has a great advantage over others in that it is not technically difficult and is a well known operation for other diseases of the rectosigmoid colon.

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Refer to: Carey JS, Plested WG, Scott C: Cardiac valve replacement—The rationale for earlier operation. West J Med 121:274-280, Oct 1974

Cardiac Valve Replacement

The Rationale for Earlier Operation

JOSEPH S. CAREY, MD, WILLIAM G. PLESTED, MD, *and* CALVIN SCOTT, BS, *Los Angeles*

BECAUSE OF THE HIGH RISK of cardiac valve replacement, operation is usually delayed until incapacitating (functional class III) symptoms develop. Since 1966, however, operative mortality has decreased to approximately 5 percent in many reported series (Table 1). In addition, improved prosthetic materials have significantly reduced valve-related complications. The most common cause of death after cardiac valve replacement has been myocardial failure rather than dysfunction of the prosthetic device.[1-6] Under ideal conditions, such as the absence of severe myocardial failure, the risk of valve replacement should be relatively low.

At Wadsworth Veterans Administration Hospital, single or double valve replacement was performed in 138 consecutive patients from October 1, 1966 through October 1, 1972. Although all but a few patients had functional class III or IV disease, and many were operated upon in emergency, the hospital mortality was low (Table 1). Four of the five hospital deaths were due to preventable technical errors. These results suggest that the risk of cardiac valve replacement may indeed be lower than it is commonly thought to be. An analysis of the late results in this series of patients, all of whom have now been followed at least one year, indicates that functional rehabilitation is frequently not achieved. The relatively poor long-term results suggest that delaying operation may inhibit functional rehabilitation.

This report examines the operative techniques which were used to obtain the gratifying early results. In addition, the long-term functional results are analyzed, and we question the rationale of delaying operation until patients reach functional class III status.

From the Thoracic Section, Surgical Service, Veterans Administration Wadsworth Hospital Center, and the UCLA School of Medicine, Los Angeles.

Submitted April 22, 1974.

Reprint requests to: J. S. Carey, MD, Santa Monica Medical Plaza, 1260 Fifteenth St., Santa Monica, CA 90404.

Cardiac valve replacement (single or double) was carried out in 138 consecutive patients with valvular heart disease over a six-year period at the Wadsworth Veterans Administration Hospital. All but a few had functional class III or IV disease. Hospital mortality was 3.6 percent.

Normothermia, coronary perfusion and beating of the heart were maintained throughout the procedure. All patients were followed at least one year and the average follow-up was four and a half years. The late mortality was 27 percent. Seventy-five percent of the late deaths were due to progressive cardiac disease. The mortality due to prosthetic valve dysfunction was 4 percent.

Subjective evaluation of survivors revealed that a high percentage remained symptomatic. Only 50 percent of the total group of patients were significantly improved.

The high incidence of late mortality and poor long-term functional results are contrasted to the low operative risk and improved reliability of prosthetic valves. The rationale of delaying operation until functional class III limitation develops is questioned. Earlier operation is recommended before irreversible myocardial hypertrophy and fibrosis develop.

Clinical Material

All patients undergoing cardiac valve replacement for valvular heart disease operated upon by the authors between October 1, 1966, and October 1, 1972, were included in the series. In no case was operation withheld because of severity of disease. Patients undergoing cardiac valve replacement together with correction of associated lesions (aortic aneurysm, coronary artery stenosis, congenital lesions) were not included. All patients had functional class III or class IV disease (New York Heart Association) at the time of operation, except for three who underwent replacement of a previously implanted prosthetic device for multiple embolic episodes. All but two were men. Clinical data revealed that 79 percent were or had been cigarette smokers and the majority were social users of alcohol. The average age at the time of operation was 48 years. In most instances, the patients had been followed for many years in the Cardiology Clinic. Operation was done when incapacitating symptoms which were refractory to medical therapy developed. The decision to operate was made at a conference of the same group of cardiologists and surgeons throughout the study period.

Surgical Technique

Cardiopulmonary bypass was carried out with an Olson pump and a disposable bubble oxygenator (Bentley Laboratories, Santa Ana, California), except in a few cases early in the series in which a rotating disc (Kay-Cross) oxygenator was used. Left ventricular vents and normothermic perfusion were used in all cases. The oxygenator was primed with a mixture of balanced electrolyte solution and colloid (usually whole blood and albumin).

Aortic valve replacement was performed through a median sternotomy using continuous normothermic coronary perfusion, permitting the heart to beat throughout the procedure. The aorta

TABLE 1.—*Data on Hospital Mortality in Various Series of Cardiac Valve Replacement*

Reference	*Time Period*	*No. of Patients*	*Valve Replaced*	*Prosthetic Valve*	*Hospital Mortality (percent)*
Messmer[1]	1969-1971	460	Aortic	Bjork-Shiley	8.5
Henze[2]	1969-1972	161	Aortic	Bjork-Shiley	5.0
Behrendt[3]	1971	252	Aortic, Mitral, Double	Starr-Edwards	5.5
Griepp[4]	1971-1972	146	Aortic, Mitral, Double	Starr-Edwards	4.7
Pacifico[5]	1967-1970	304	Aortic	Starr, Homograft	6.2
Cooley[6]	1971-1972	138	Mitral, Mitral and Aortic	Cooley-Cutter	5.8
Present Series	1966-1972	138	Aortic, Mitral, Double	Starr-Edwards	3.6

was opened through a transverse or slightly oblique aortotomy without entering the coronary sinus. Coronary perfusion catheters (Mayo balloons) were anchored in place with one 5-0 suture through the aortic wall. In calcified aortic valves no effort was made to remove calcium deposits located in the aortic or myocardial wall. In such instances heavy sutures were placed through the calcium and then into the prosthesis. Interrupted figure-8 horizontal mattress sutures of 2-0 Tevdek, 4 to 6 in each valve cusp, were used to anchor the prosthetic valve in place. Starr-Edwards valves were used for aortic valve replacement in all instances. From November 1967 on, only cloth-covered models have been used. The aorta was closed with a continuous 4-0 Tevdek suture leaving the coronary perfusion catheters in place as long as possible. A Foley catheter was passed through the valve into the left ventricle during aortic closure. At the uppermost point of aortic closure, a final mattress suture was placed around the coronary catheters. At this point the left ventricular vent was clamped and the heart allowed to fill with blood. The coronary perfusion catheters were then removed and the remainder of the aortic incision closed. As soon as the aortotomy was closed the aortic cross clamp was removed. Using this technique, coronary perfusion was interrupted only for the minute or two necessary to close the remainder of the aortotomy incision. The patient was then immediately weaned from cardiopulmonary bypass.

When both aortic and mitral valve replacement were performed, coronary perfusion was instituted at the beginning of the procedure and continued during the replacement of both valves.

Mitral valve replacement was also performed through a median sternotomy. After institution of cardiopulmonary bypass, the aorta was cross-clamped and the left atrium was opened through an incision in the posterior inter-atrial groove. The anterior leaflet of the mitral valve was incised and the anterior row of sutures was placed while traction was held on the partially excised valve. The aortic cross-clamp was removed after 10 minutes, and the sutures were placed into the prosthetic valve. The natural valve was then completely excised and the posterior row of sutures was placed, with another brief period of aortic cross-clamping if necessary. Figure of 8 mattress sutures of 2-0 Tevdek were used to fix the valve in place. Starr-Edwards prosthetic valves were used in all instances for mitral valve replacement. After January 1968, only cloth-covered models were used. During closure of the atriotomy incision, a Foley catheter was left in place to keep the prosthetic valve inoperative. When closure of the atriotomy was completed, the catheter was removed and all air evacuated from the heart through the apex of the left ventricle by way of the left ventricular vent.

The tricuspid valve was also approached through a median sternotomy. Valve replacement was accomplished by techniques similar to those employed for mitral valve replacement. However, only Bjork-Shiley prosthetic valves have been implanted in the tricuspid position.

Postoperative Care

All patients were monitored in the intensive care unit for 3 to 5 days after operation. Standard variables were monitored during the first few postoperative days, including arterial pressure, central venous pressure, arterial blood gases, blood volume and hourly urine output. Left atrial pressure measurements were not employed. Because of the use of hemodilution perfusion, fluid intake was kept at a minimum during the first few postoperative days and urine output was maintained with furosemide or ethacrynic acid. The liberal use of these diuretic agents has greatly reduced need for tracheotomy in the postoperative period. It is, however, important to replace potassium losses caused by the use of diuretic drugs. We have

TABLE 2.—*Death in Hospital and Late Mortality after Starr-Edwards Valve Replacement*

	No. Pts.	Hosp. Mort.	Late Mort.
Single valve replacement			
Aortic	66	1	16
Mitral	55	3	15
Tricuspid	1	0	0
Total	122	4(3.3%)	31(25%)
Multiple valve replacement			
Aortic and mitral	13	1	4
Mitral and tricuspid	3	0	1
Total	16	1(6.3%)	5(31%)
Combined single and multiple	138	5(3.6%)	36(27%)

TABLE 3.—*Causes of Hospital Mortality*

Procedure Valve Replacement	*Cause of Death*
1. Aortic	Mesenteric infarction
2. Aortic and mitral	Right coronary artery dissection
3. Mitral	"Low cardiac output"—Prosthesis too large
4. Mitral	Retrograde aortic dissection
5. Mitral	Postoperative cardiac tamponade

found that the urinary concentration of potassium averages 40 to 50 mEq per liter during diuresis induced by ethacrynic acid.

Methods of Data Review

Medical information was digitized on data transcription sheets, and computer analysis was performed at the Western Research Support Center of the Veterans Administration (Sepulveda, California). Follow-up data were obtained by questionnaires sent to patients or by direct contact with the family or physicians. Causes of death were determined from clinical data or autopsy information.

Questionnaires were returned by 94 of 97 survivors. Information was obtained from relatives or clinical records on the 3 remaining patients. One patient was lost to follow-up nine months after operation. Functional class was determined by evaluating the patient's ability to climb stairs and walk level distances, and by symptoms and subjective sense of improvement. If the patient's activity was essentially unlimited and he was asymptomatic or mildly symptomatic and (subjectively) greatly improved, he was considered to be Class I. A patient who could not climb more than two flights of stairs or walk two level blocks without stopping but was minimally symptomatic and felt greatly improved was considered Class II. A patient who was limited to the same functional activity but was moderately symptomatic and considered himself only slightly improved was reported as Class III.

Results

Survival

The hospital mortality was 3.3 percent for single valve replacement, and the late mortality was 25 percent; for multiple valve replacement, 6.3 and 31 percent respectively (Table 2).

The causes of hospital death are listed on Table 3. All deaths occurred postoperatively; there was no patient who could not be removed from cardiopulmonary bypass. Among 79 patients undergoing aortic valve replacement alone or in combination with mitral or tricuspid replacement, there were 2 hospital deaths: one was caused by technical errors in the use of coronary perfusion and the other was caused by diffuse mesenteric infarction which occurred after isolated aortic valve replacement for aortic insufficiency. Three patients died after mitral valve replacement; all three deaths were due to technical errors occurring at the time of operation. In one patient who died of "low cardiac output," indentations from the cage of the prosthetic valve and hematoma formation were found on the interventricular septum at autopsy, indicating the prosthetic device was too big. Retrograde aortic dissection occurred after institution of emergency cardiopulmonary bypass in another patient; although bypass was reinstituted through the ascending aorta, cerebral damage occurred which eventually led to the patient's death. The third death was caused by cardiac tamponade occurring 10 days postoperatively which was erroneously treated as pulmonary embolism.

The causes of late death are listed by categories in Table 4. There were no definite valve-related deaths after aortic valve replacement, but four late valve-related deaths occurred after mitral valve replacement, and one after aortic and mitral replacement. There were two instances of thrombus formation found at autopsy on a prosthetic mitral valve, which probably led to the patients' death; one occurred in a patient with a Model 6500 series (low-profile) Starr-Edwards valve, and the other in a patient with a 6300 series (early cloth-covered model) valve. Neither of these devices are currently in use. A third patient died of a splenic hemorrhage probably caused by embolism. A model 6120 (silastic ball) prosthetic valve was

TABLE 4.—*Causes of Late Death 3 Months to 6.3 Years (Average 2.3 Years) after Hospital Discharge*

	Aortic	*Mitral*	*Multiple*	*Total*	*Autopsy*
Prosthetic failure	0	4	1	5	5
Non-cardiac	3	4	1	8	8
Progressive cardiac disease	7	2	2	11	8
Unknown	6	5	1	12	1
Total	16	15	5	36	21(60%)

TABLE 5.—*Significant Non-Fatal Postoperative Complications During Hospitalization*

	Aortic	*Mitral*	*Multiple*	*Total*
Arrhythmia	27	29	7	63(46%)
Respiratory	8	11	2	21(15%)
Tracheostomy required	4	6	4	14(10%)
Low cardiac output "syndrome"	5	3	5	13(9%)
Stroke with residual	4	0	1	5(4%)

TABLE 6.—*Significant Valve-Related Complications*

	Aortic	*Mitral*	*Multiple*	*Total*
Mortality	0	5	1	6(4.1%)
Reoperation	2	2	1	5(3.6%)
Stroke with residual	6	3	0	9(6.5%)

TABLE 7.—*Subjective and Functional Results in Survivors at the End of the Current Follow-up Period*

	No. of Patients	*Percent of Survivors*
Subjective result		
Greatly improved	39	40
Slightly improved	28	29
Not improved or worse	20	21
Unknown	10	10
Functional result		
Class I (NYHA)	31	32
Class II	38	39
Class III	27	28
Class IV	0	0
Lost to follow-up	1	1

used in this patient. The fourth valve-related death also occurred in a patient with a 6120 series valve, in whom periprosthetic leak occurred. The fifth value-related death occurred after aortic and mitral replacement with model 2300 (aortic) and 6300 (mitral) prosthetic valves. Several patients died of non-cardiac causes, including bowel obstruction, malignant disease, and trauma. The most common cause of late death was "progressive cardiac disease." In most of these patients, clinical and autopsy findings indicated normal functioning of the prosthetic valve. A significant number of patients also died of undetermined causes. In these cases, clinical and autopsy information was not adequate to clearly determine the cause of death.

Postoperative Complications

Postoperative complications occurred in the majority of patients (Table 5). Some type of arrhythmia occurred in nearly half of the survivors. Significant respiratory complications occurred in 15 percent, and tracheostomy was required in 10 percent. Low cardiac output "syndrome" (poor peripheral perfusion, low urine output, vasopressors required) occurred in 9 percent of patients. Five patients had neurological damage upon awakening from anesthesia after aortic or aortic and mitral valve replacement. The neurological damage was major (accompanied by paralysis) in only one of the five. Although these strokes are thought to be due to calcium or air embolism, the possibility of embolism from the prosthetic valve cannot be ruled out.

Prosthetic Valve-Related Complications

All the known valve-related complications are listed in Table 6. There were one early and four late valve-related deaths after mitral valve replacement, and one late valve-related death after aortic and mitral replacement (discussed above). All six occurred with prosthetic valves now no longer in use (models 6120, 6500, 6300, and 2300). Five patients required reoperation, three for periprosthetic leak (two aortic, one mitral) and two for removal of early model cloth-covered prostheses which were thought to be obstructive (one aortic, one mitral). There were nine clear episodes of postoperative embolism with neurological residual: eight of the patients have minor weakness or memory loss, and one is bedridden with hemiplegia. All episodes occurred in patients with earlier model prosthetic valves.

Functional Results in Survivors

As determined by subjective and functional results 69 percent of patients were improved and 71 percent were in Class I or Class II (Table 7). A relatively large proportion of patients in the current series felt "not improved or worse," and 28 percent were in functional Class III postoperatively.

Discussion

The occurrence of myocardial failure of uncertain origin in the early postoperative period after cardiac valve replacement has been noted by

several investigators. Various types of "myocardial necrosis" have been described, including a concentric type of subendocardial necrosis,[7] and a diffuse, patchy distribution of hemorrhage and necrosis.[8] The absence of these findings in the present series suggests that some aspect of surgical techniques we used may have prevented the development of myocardial necrosis. The most likely explanation is that our use of normothermic coronary perfusion, allowing the heart to beat throughout the operative procedure, either minimized or eliminated the occurrence of myocardial damage during operation. There is evidence that the use of electrical fibrillation for prolonged periods may produce myocardial hemorrhage and necrosis.[9] In addition, spontaneous fibrillation, which may occur during hypothermic coronary perfusion, may also damage the myocardium. Ischemic arrest may be well tolerated for 30 to 45 minutes in the normal heart, but the hypertrophied heart tolerates ischemia poorly, as was indicated by experimental evidence in dogs.[10] Cooley and coworkers[11] reported an operative mortality of 52 percent in patients in whom ischemic arrest was employed during aortic and mitral valve replacement for aortic stenosis and mitral stenosis. Kirklin's group,[5] on the other hand, reported an operative mortality of 6.2 percent after aortic valve replacement procedures in which mild hypothermia, coronary perfusion and a beating heart were used. Topical hypothermia has also been associated with low hospital mortality, particularly using cold saline rather than ice in the pericardial well.[5,12]

The patients in this series were drawn from a relatively fixed hospital population so that preselection, such as may occur in a referral practice, is not a factor in determining the quality of clinical material. In many instances, Veterans Administration Hospital patients are poorer surgical risks because of delay in obtaining medical care, resulting in the development of advanced disease before they come to the hospital. In addition, most male veterans are heavy smokers and users of alcohol. No patient was refused operation, however, because of severity of disease or because of the presence of high surgical risk.

In spite of the absence of pre-selection and the inclusion of all patients as surgical candidates regardless of "risk," the hospital mortality for this series is lower than that reported from other major centers. This is strong evidence that the use of normothermic coronary perfusion, and the avoidance of prolonged ischemic arrest and electrical or spontaneous fibrillation, provides the best "myocardial protection" during cardiac valve replacement.

The high mortality and sub-optimal subjective and functional results obtained in this series are disconcerting. However, very little late morbidity seems to be directly related to the prosthetic valves. Six of the 16 valve-related complications were due to technical errors (selection of too large a prosthetic valve, periprosthetic leak), and the majority of the remaining complications occurred in patients with earlier model valves. Current data indicate that the present model Starr-Edwards valves (2310-2320 aortic, 6310-6320 mitral) are hemodynamically satisfactory.[13] These models were used in the last 48 patients of this series, and no definite valve-related complications have occurred in this group.*

Most of the late mortality in this series was related to progressive cardiac disease. This suggests that operation may have been performed too late in the course of the disease. Irreversible congestive heart failure and ventricular hypertrophy may already be present at the time of operation. In spite of moderate improvement by valve replacement, symptoms eventually recur; in such patients, the clinical condition may temporarily stabilize, but deterioration then occurs. Other patients may die suddenly of unknown causes within the first two years. In most such cases there was pronounced left ventricular hypertrophy or dilatation at the time of operation. Although it is possible that death in some of these cases may have been related to prosthetic failure, progression of irreversible myocardial failure seems to be a more likely possibility.

In order to improve late mortality as well as functional results, earlier operation would seem to be indicated in some patients, particularly those with aortic valve disease or mitral regurgitation in whom severe, perhaps irreversible, left ventricular failure is likely to develop at any time. In a previous study, we found that the late mortality of mitral stenosis was considerably less than that of mitral regurgitation.[14] This finding, which has been reported by other investigators,[15] also suggests that

*As of April 1, 1974, 100 patients had had replacement of aortic or mitral valves, or both, using current model Starr-Edwards devices. One hospital death was definitely valve-related (cerebral-embolus), and autopsy evidence of mild thrombus formation was found in a second patient who died of chronic congestive heart failure. Three late deaths occurred suddenly and autopsy was not performed. No evidence of embolism, thrombus formation, infection, periprosthetic leak or cloth wear has been found in the remaining patients in this series. Definite valve-related complications have thus occurred in 2 percent of patients receiving current model cloth-covered Starr-Edwards valves.

earlier operation should be performed in patients with left ventricular overload.

Future patients may be benefited by more precise studies of ventricular function. For example, the routine use of non-invasive studies such as echocardiography may allow the identification of critical increases in left ventricular mass before the development of irreversible cardiac failure.

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ERNEST K. GOODNER, MD
EMIL A. TANAGHO, MD, M Ch
BARBARA PRINCE, MSW
BYRON C. PEVEHOUSE, MD
PETER COHEN, MD

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Refer to: Specht EE, Goodner EK, Tanagho EA, Prince B, Pevehouse BC, Cohen P: Myelomeningocele—A symposium on orthopedic, ophthalmologic, urologic, psychological and social, neurosurgical and general considerations (Pediatric Rounds). West J Med 121:281-304, Oct 1974

Myelomeningocele

A Symposium on Orthopedic, Ophthalmologic, Urologic, Psychological and Social, Neurosurgical and General Considerations

Refer to: Specht EE: Myelomeningocele—Part 1: Orthopedic management in children, *In* Myelomeningocele—A symposium. West J Med 121:281-291, Oct 1974

Myelomeningocele—Part I

Orthopedic Management in Children

ELMER E. SPECHT, MD, *San Francisco*

If an infant with myelomeningocele survives, the goals of orthopedic management are (1) a straight spine and straight legs and feet, (2) mobile hips, (3) a pull-to or swing-through gait and (4) maximum possible self-sufficiency, including whatever can be accomplished by vocational training at an appropriate age. Helping the patient to attain these goals depends on informed evaluation of the expected functional capacity in relation to a given neurological deficit, and assessment of the likelihood of fixed deformities related to muscle imbalance and positional contractures. Familiarity with techniques for correction of deformities and for habilitation, with specific reference to walking —if that is a realistic goal—are also essential.

One of the most important responsibilities of the orthopedic surgeon evaluating these children is to determine the pattern of remaining neurological function and the presence of functioning or spastic muscle groups, as well as the status of their antagonists, and to anticipate subsequent deformity (Table 1). It does not necessarily follow from the fact that an infant has been born with myelomeningocele that there will be handicapping neurological impairment. In a study published in 1961, Doran and Guthkelch[1] reported 307 cases followed for a minimal period of two and a half years. They found that of 95 survivors after treatment of myelomeningocele with and without hydrocephalus, 66 showed either no paralysis or no more than minor weaknesses in the lower extremities, even though sphincter paralysis was frequently present. Comparable findings were more recently reported by Piggot,[2] in whose series 32 of 108 babies with myelomeningocele (but without spinal fluid leak and without hydrocephalus at birth) showed no detectable muscle weakness at birth.

Part I of an article in six parts.

From the Department of Orthopaedic Surgery, University of California, San Francisco.

Reprint requests to: E. E. Specht, MD, Department of Orthopaedic Surgery, University of California, San Francisco, San Francisco, CA 94143.

TABLE 1.—*Correlation of Neurological Level, Remaining Muscular Function, and Deformity or Disability Most Commonly Encountered in Myelomeningocele*

Level Intact	*Principal Motor Groups Remaining Functional in Legs*	*Principal Motor Groups Paralyzed or Weak in Legs*	*Deformities and/or Disabilities of Spine and Legs Due to Muscle Strength Imbalance (Positional Deformities May Be Superimposed)*
T_{12}			Spinal scoliosis or lordosis
	None	Complete lower-extremity paralysis	Coxa valga, occasional hip subluxation
L_1-L_2			Spinal scoliosis or lordosis
	Hip flexors fair to good Hip adductors poor to fair	Hip extensors paralyzed Hip abductors paralyzed Knee and foot flail	Flexion-adduction contracture of hip, with subluxation frequently, dislocation occasionally
L_3-L_4			Lumbar lordosis or scoliosis
	Hip flexors normal Hip adductors good to normal Quadriceps fair to good Tibialis anterior trace to fair	Hip extensors paralyzed Hip abductors paralyzed Knee flexors paralyzed Triceps surae paralyzed Foot evertors paralyzed Foot invertors paralyzed	Flexion-adduction-external rotation contracture of hip early; hip dislocation at birth or early Extension contracture of knee occasionally Severe, progressive calcaneus of foot
L_5			Lordosis, scoliosis
	Hip flexors and adductors normal Quadriceps normal Medial hamstrings fair to good Foot dorsiflexors and invertors normal	Hip extensors trace to poor Hip abductors poor to fair Triceps surae paralyzed Foot evertors fair	Flexion-adduction contracture of hip; coxa valga, subluxation or dislocation common Knee flexion-internal rotation contracture Severe progressive calcaneovarus of foot
S_1-S_2			Lordosis, scoliosis
	Hip nearly normal except extensors Knee good except lateral hamstrings Foot and ankle extrinsics good to normal except toe flexors	Hip extensors fair to good Biceps femoris fair Foot intrinsics paralyzed Toe flexors fair	Occasional subluxation of hip Planovalgus foot, claw toes

In the treatment of deformity due to myelomeningocele, it is vital to recognize that the deformity caused by dynamic, occasionally spastic,[3] muscle imbalance differs from the relatively static situation one often encounters in deformities caused by old poliomyelitis. Deformity may progress slowly because a minimal imbalance of forces may be acting over a prolonged period of time. The concept of a child who is a *growing paraplegic* is useful in understanding this tendency to slow progression of deformity. Serial evaluations throughout childhood are essential.

Deformities of the Foot and Ankle

Orthopedic management of the foot (as well as of the spine, hips and legs) in myelodysplasia must always be directed toward the ultimate goals of the educability and employability of the patient. A mobile, plantigrade, balanced, shoeable foot is essential, and one of the responsibilities of the orthopedist, as elsewhere in the management of this disorder, is to determine the level or pattern of remaining neurological function and to predict the type of deformity which this pattern can be expected to produce. Thus, with a functional fourth lumbar level, the tibialis anterior muscle may be innervated, but its action may be unbalanced by functioning plantar flexors and evertors. A varus force may be produced; but more important, a progressive and severe calcaneus deformity may develop, which can be minimized by early transfer of the tibialis anterior tendon to the heel. With a functional fifth lumbar level, a calcaneus deformity will almost certainly develop if tendon transfer is not done by the time the patient is one to two years old, and at present no satisfactory means of managing a fully developed calcaneus deformity exists. At the first and second sacral levels, ankle plantar flexors and foot evertors will be functioning, so that clawing of the toes and a planovalgus foot are more common deformities. At the third sacral level, intrinsic muscular

imbalance obtains and a cavus foot is most likely. The equinus portion of the deformity that is commonly present is a positional rather than a dynamic problem and is thus less apt to recur after tenotomy. All dynamic deformities, however, must be brought into balance by neurectomies, tendon transfers or tendon releases; otherwise recurrence is a certainty.

The two deformities of the foot in myelodysplasia which most commonly require correction are equinovarus and equinocavovarus.[4-6] Opinion on the management of these deformities varies. Sharrard[6-9] feels that splinting, manipulation and serial plaster casting for these insensitive feet result in disaster. Hayes, Gross, and Dow,[5] Tzimas[10] and Walker,[11] on the other hand, believe that such measures are useful. However, all of these authors warn against the injudicious use of plaster on feet in which sensation is lacking, and all resort to the use of surgical procedures if necessary in order to obtain correction. Sharrard and Grosfield[6] have reported the results of their management of 241 feet with various deformities; they found soft-tissue releases and tendon transfers to be most effective. For equinovarus deformity they advised medial and posterior releases; their rate of success in this group was 22 percent. Usually, the tendo achillis, both long toe flexors, both tibial tendons and the medial ligaments of both the ankle and the subtalar joints will require division. An unopposed tibialis anterior tendon should be transferred to the lateral side of the foot if no tendency to calcaneus deformity is present; if it is, the tendon should be transferred posteriorly. For simple equinus contracture, subcutaneous tendo Achillis tenotomy and toe flexor tenotomy will often suffice.

Talectomy may also be of value in the management of rigid feet in which equinovarus deformity cannot be controlled and the potential for walking is limited. Menelaus[12] reported on his use of this procedure in 14 feet with equinovarus deformity due to spina bifida. He believes that best results can be obtained if talectomy is done between the ages of one and five years, but that triple arthrodesis is preferable for the older child or adult.

Planovalgus and equinovalgus feet are also commonly seen in myelodysplasia, and convex pes valgus (vertical talus) has been described.[13] The Grice subtalar arthrodesis is useful in the correction of planovalgus deformity. Paralytic vertical talus is a difficult deformity to manage. Dorsolateral release with open reduction is indicated, along with such tendon transfers as are necessary to bring the musculature of the foot into balance.

The fully developed calcaneus and calcaneovarus deformities which the clinician occasionally encounters are among the most difficult to correct. In cases in which an unbalanced overpull of the peroneus tertius, the tibialis anterior, or both, cause an elevation of the arch, both tendons should be transferred through the interosseous membrane to the heel at the midline of the foot. These tendons are usually not sufficiently strong to act as plantar flexors or to cause equinus deformity, but in the event that equinus ensues, this deformity is more easily held by a dropfoot brace, whereas a calcaneus deformity cannot be held by any brace. These transfers should be done when the child is about a year old.

In order to salvage some feet, triple arthrodesis may be necessary, but this procedure should not be undertaken lightly. Nonunion after attempted triple arthrodesis has occurred in nearly one-third of cases in some series.[5] It should also be borne in mind that in the past, at least, osteomyelitis in insensitive feet has often required amputation in order to control the infection. Pantalar arthrodesis should be avoided; unwanted ankle motion can be controlled by the placement of appropriate anterior and posterior stops on short leg braces. Neuropathic arthropathy may occur after attempted arthrodesis of joints, especially the ankle; furthermore, even if fusion is accomplished, there is no virtue in a completely rigid ankle and hindfoot.

Finally, it must be stressed that nonplantigrade feet, particularly those that have been immobilized in plaster casts, but also those that have been supported by braces for prolonged periods of time, are vulnerable to trophic ulceration. Casts, if they are used at all, must be well padded and bivalved; removable splints are preferable. Skin should be inspected for rubor at pressure points at least twice daily. It is better to maintain a surgically induced correction by passive movement of the involved joint than by the use of plaster. It is also better to obtain a correction by passive manipulation and to maintain it by plaster splints, if necessary, than to attempt plaster correction of deformity as one might in congenital clubfoot with normal skin sensation.

Deformities of the Knee

Although Carr[4] states that the most common knee deformity in his series was knee flexion contracture, which he attributed to strong hamstrings

and calf muscles opposed by a weak quadriceps, it is generally agreed that hyperextension deformity occurs more frequently, especially when the third lumbar segment is functioning; the result is a nearly normal quadriceps with weak knee flexors. Sharrard[9] advocates early elongation of the quadriceps to allow at least 45 degrees of knee flexion in severe cases. Hayes and associates, on the other hand, feel that serial plaster casting in infancy will allow sufficient correction that a long leg brace will permit ambulation later. They recommend transfer of the hamstring tendons to the femoral condyles in those instances of knee flexion deformity due to myelodysplasia with spasticity, as in cord traction syndromes. Derotational osteotomy of the tibia is occasionally indicated. Supracondylar femoral osteotomy for persistent contracture in patients over the age of eight may also be useful, and of more permanent benefit, than simple posterior knee release for positional flexion contracture.

Paralytic Dislocation of the Hip

The problem of paralytic dislocation of the hip has been studied in considerable depth by Sharrard,[14] who found that hip dislocation did not occur if there was complete paralysis of all hip musculature. If the first, or first and second, lumbar segments were functioning, moderate or severe subluxation, in association with progressive flexion-adduction deformity and coxa valga, developed in the first year of life in 58 of 70 hips. An additional eight in this group were dislocated.

The most striking incidence of dislocation, however, occurred in the group in which the upper three or four lumbar roots were intact, with strong hip flexors and adductors but complete paralysis of the extensors and abductors. In this group, dislocation was either present at birth or developed in the first year of life in 72 of 85 limbs, and the remaining 13 were subluxed, in spite of normal development of the acetabulum.

In the group in which all five lumbar segments were functioning normally, with good hip musculature except for weak abduction and paralyzed extension, the picture was similar to that in which the first and second segments were functioning; a slowly progressive flexion-adduction contracture developed, with subluxation of 12, and dislocation of 7, limbs in the group of 27 with this pattern. If hip extension only was weak, no deformity was seen at birth except for mild fixed flexion in some infants, who did not, however, have dislocated hips. No subluxation or dislocation was seen when innervation of the limb was intact.

Sharrard's proposed remedy for this problem was posterolateral transplantation of the iliopsoas. In 1964 he reported[14] that he had done 150 such procedures on children between the ages of four months and 17 years, the mean age being three years. His initial report was quite enthusiastic, and numerous "Sharrard procedures" have been done subsequently.[15] In a recent long-term follow-up study,[16] however, it became evident that this procedure probably has very limited applications. Indeed, one prominent children's orthopedist has recently termed it "the necrotizing iliopsoas transfer." Carroll and Sharrard's recent findings were that instability of the hip persisted in 40 percent of cases at review five to ten years postoperatively, and that in the absence of gluteal muscles the transplanted muscle was unlikely to provide abduction or extension against gravity (in other words, it had poor-grade strength). They state that the most consistent reason for late instability was failure to obtain a concentric reduction at the time of operation. They feel it important to restore muscle balance and, in addition to carrying out indicated procedures, to correct dysplasia or maldirection of either the acetabulum or the femur, as well as to correct coxa valga. In this context it should be stated that Salter[17] does not feel that his technique of innominate osteotomy is indicated in the paralytic dislocation of myelomeningocele. Carroll and Sharrard's conclusion was that with high paraplegia, neonatal dislocation, and acetabular dysplasia, the 25-percent risk of avascular necrosis did not justify more than such soft-tissue releases as are necessary to permit bracing. They continue to feel that, with lower lumbar levels of paralysis and a better prognosis for ambulation, the procedure is justified. Similar findings have been reported by Rueda and Carroll[18] in 21 children with 30 iliopsoas transfers, 15 by the Sharrard and 15 by the Mustard technique. In this series only 10 of the 30 hips operated on remained stable at review one to eight years after transfer, and active power of abduction was poor. A surprising finding was that the power of hip flexion remained strong in 22 hips in spite of transfer of the major hip flexor.

Cruess and Turner[19] in 1970 reported their results with the use of Mustard's iliopsoas transfer through an anterior window cut in the ilium. Their indications were (1) severe abductor lurch in the presence of a strong hip flexor, (2) flexion con-

tracture of the hip due to muscle imbalance and (3) muscle imbalance leading to progressive valgus of the femoral neck. It must be noted that they list two contraindications to the procedure: (1) absence of other active hip flexors and (2) subluxation or dislocation of the hip. In either of these cases the transfer should be done only as an adjunct to some procedure that corrects the posterior acetabular defect. Eight of 13 somewhat older patients, 7 to 15 years of age, were benefited functionally, according to this report, in spite of the fact that all transferred muscles lost some force. Essentially similar results were reported by Freehafer, Vessely and Mack[20] in a larger series in which they used a modification of the Mustard technique. They stated that all but seven of 52 hips improved, but it was their impression that the success of the transfer was more related to removal of a deforming force than to the strength of the transferred tendon. Broome and Basmajian[21] have shown that electrical activity of the transferred muscle can be lost; three of seven transfers resulted in greatly reduced activity.

Hayes, Gross and Dow[5] have had a similar experience in treatment of paralytic dislocation of the hip. They concur with Sharrard that varus osteotomy as suggested by Jones[22] and the rotation-adduction osteotomy advocated by Somerville[23] are not adequate in the face of muscular imbalance. Donaldson[24] and Tzimas[10] have also advocated iliopsoas transfer and have used it in conjunction with Salter's innominate osteotomy.

Hogshead and Ponseti[25] have approached the same problem in a different manner. It is their opinion that dislocation of the hip is related to contracture of the iliotibial band rather than to muscle imbalance. Proceeding on this theory, they have transferred the distal end of the iliotibial band subfascially across the buttock and sutured it to the lumbodorsal fascia just lateral to the spine at the level of the third or fourth lumbar vertebra. The proximal end is left anchored to the greater trochanter, and an anterior hip release is done at the same time if there is any flexion contracture of the hip. In addition they incise the lumbodorsal fascia if there is fixed lumbar lordosis. They had done this in nine cases of myelomeningocele when they reported in 1964. Their patients were between three and a half and ten and a half years of age at the time of surgery, and they stated that they obtained an average of 79-percent relief of the flexion deformity. Of the 13 hips which were dislocated or subluxed preoperatively, 11 were improved and only one remained dislocated. They have found that the procedure results in a dynamic fasciodesis, but that few of the patients were able to discard canes or crutches after the operation. They claim, however, that better stance and easier gait result. No recent follow-up on this procedure has been forthcoming.

Others have suggested that transfer of the adductors to the ischial tuberosity in addition to transfer of the iliopsoas may be necessary to bring the hip into stable muscle balance. All authors agree that whatever is done, mobility of the hip must be maintained at all costs, and it would appear that dislocated mobile hips are preferable to reduced immobile ones. It may even be that a much more conservative approach will prove useful; in a preliminary report, McKibbin[26] has expressed the opinion that abduction-internal rotation splinting from an early age may obviate the need for surgery in some cases. It should always be recalled that as adults, very few if any patients with bilateral paralysis below the second lumbar level will be functional walkers, and that if surgery of this magnitude is contemplated, it should be so timed that school progress is not interfered with. Children with one or both hips dislocated can still ambulate well, and although stability is highly desirable, a minimum of 90 degrees of flexion is essential.

Deformities of the Spine and Pelvis

Spinal and pelvic deformity in childhood and adolescent paraplegia have been extensively studied by Kilfoyle, Foley and Norton.[27] In 1965 they reported their experiences with 107 children and adolescents who had been admitted for either congenital or acquired paraplegia. Of this group, 73 had congenital paraplegia, and of the entire group all but 10 had significant spinal deformities. The authors stated that with deforming forces at work from birth, every possible deformity in the spine and pelvis was encountered. These ranged from kyphoscoliosis so severe that only the prone position could be assumed to minimal excessive lumbar lordosis. Forty-seven of the deformities were lordosis, scoliosis or kyphosis alone, and the remainder were combinations of the three, with one being the major deformity.

In this series, lordosis was the predominant or major deformity, and it occurred in 47 of the 97 patients with spinal deformity. In a total of 80 there was some lordotic deformity of greater or

lesser degree, either alone or in association with other deformities. The authors found that there was a distinct correlation between the level of the lordosis and the state of balance. In 19 patients with lower-level lordosis and paralysis at or below the third lumbar segment, none were completely off-balance and only five of the group were found to be partly balanced. All of these five had gluteus maximus paralysis and four had either dislocation or subluxation of the hip. In the group of patients with spinal cord involvement from the third lumbar segment down to the sacrum, lordosis, hip flexion contracture and dislocation are the preponderant deformities.

In this series there were 36 patients who had scoliosis as a predominant deformity. Of these, two were well balanced, 27 were partially balanced, and seven were completely off-balance (unable to sit or stand without support). The authors noted that in the partially balanced patients the ability to walk was affected primarily by the lordosis, whereas the scoliosis had a direct effect on the ability of the patient to sit easily and use both hands while sitting. Of the seven patients who were completely off-balance, all but one were so deformed and rigid that correction was impossible. These authors believe that this state of affairs is preventable. An attempt to relate the level of paraplegia to the incidence of scoliosis showed that there was no particular correlation and that the frequency of this deformity was about equal at all levels of paralysis. In nine patients the curve could be attributed to anomalous vertebral development with angulation. In others a chronically assumed position appeared to be a significant causative factor. In our opinion, pelvic obliquity is especially to be watched as a predisposing influence. Raycroft and Curtis,[28] in the series at the Newington Children's Hospital, found that, in those patients who had no curve at birth, more than half of those who subsequently developed scoliosis did so before age five, and almost all by age ten.

Fourteen of the 97 patients in the series of Kilfoyle and associates[27] had kyphosis and, of these, seven had congenital paraplegia. Progression of the deformity during the years of growth is common. Paraspinal muscles which become displaced anteriorly to the center of rotation of the vertebral body at the apex of the kyphos begin to act as spine flexors, and the superincumbent weight of the upper trunk and head become more effective forces as the lever arm of the cephalad portion of the spine becomes longer with growth. Standing balance may become seriously impaired or lost. Severe kyphosis may result from failure of formation of an ossification center for a vertebral body. In this case the bodies above and below converge in the space which should be occupied by the anterior half of the missing body, and this kyphosis increases with growth and becomes a hairpin curve. If allowed to progress to this extent, such a dorsal hemivertebra inevitably results in off-balance kyphosis and inability to stand, even with external support.

Rope Spine

A completely flaccid, or rope-like, spine may be seen in some instances of high-thoracic paraplegia. The spine collapses or telescopes when the patient is sitting or attempting to stand, and no external support devices are adequate. This would appear to be a clear-cut indication for spinal fusion.

Treatment of Spinal Deformity

The most commonly encountered problem is the combination of hip-flexion contracture and increased lumbar lordosis. Anterior hip release of the Soutter type, with release of all contracted structures including the iliopsoas, is indicated if there is any compromise in balance, that is, if the patient cannot stand momentarily in braces without the support of the hands on crutches. We favor a two-team approach to both hips at the same time, followed by a double spica cast for no more than three weeks to allow healing with the hips extended, and then vigorous gait training. During the period in the cast, the patient should be stood upright as much as possible—a minimum of once daily.

Treatment of scoliosis is indicated if there is any reason to suspect that a curve will progress to the point that sitting balance will be impaired. There are no hard data on the method of choice for management except that the problem of insensitive skin makes the Milwaukee brace an inappropriate solution. Most authors have favored Harrington rod instrumentation in recent years. In the future, the Dwyer anterior interbody technique may prove to be the best, in experienced hands. However, its use at the present should be limited to those centers which are studying its effectiveness. Fusion to the sacrum with the use of a sacral bar appears to be indicated if there is pelvic obliquity. Casts should not be used post-

operatively. Fusion and infection rates do not appear to be substantially different from those encountered after surgical procedures on nonparalytic curves.

Treatment of kyphosis in association with spina bifida remains an unsolved problem. Sharrard in 1968[29] reported good results in six newborn infants in whom he had done closing-wedge spinal osteotomies for severe kyphotic deformities of the lumbar spine in order to effect skin closure of the neural defect without tension. In a more recent report,[30] Sharrard and Drennan state that they have done seven more, with only one death in the intraoperative period. In two patients, the procedure failed to achieve bony union and reoperation was required. Skin problems improved in all, but there was a tendency to slow recurrence of the deformity, at a diminished rate of progression, which they attribute to the perverted flexor action of the anteriorly displaced spine extensors. James and Lassman,[31] on the other hand, have held that gross lumbar kyphosis is a contraindication to any early operative intervention.

Eyring and Wanken[32] reported in 1972 on spinal ostectomy for kyphosis in 15 children ranging in age from one day to nine and a half years. Their goals were (1) to eliminate total skin ulceration, (2) to permit supine lying and alignment of legs, (3) to permit brace wearing and ambulation and (4) to improve appearance. No patient's condition was completely corrected, although all were improved; there were no deaths and no patient lost ambulatory ability. They stated that the average blood loss during the first ten procedures was 120 percent of total blood volume, and conceded that it is "a reasonably hazardous procedure." MacEwen,[33] on the other hand, has said that he knows of several deaths caused by attempted late spinal osteotomy, and he considers it simply "hazardous." This opinion would seem to be borne out by a recent paper by Eckstein and Vora,[34] in which they report 16 cases, in patients ranging in age from newborn to eight years, with five deaths. In spite of the high mortality, they concluded that spinal osteotomy is justifiable and reasonable in cases of severe kyphosis complicated by skin problems, inability to fit braces, reduction of abdominal area such that urinary diversion cannot be done, and reduction of abdominal volume to the extent that elevation of the diaphragm with compromise of thoracic volume are significant. Sharrard and Drennan[30] also recently reported the results of spinal osteotomy in 18 additional older children (average age seven years), for similar indications, without intraoperative mortality. Union of the osteotomic site occurred in all cases, and the average correction was 33 degrees; the average loss of correction two years after operation was 11 degrees. Skin problems were said to have improved in all but two of 14 children; two who were previously unable to sit in a wheelchair were able to do so at follow-up.

It would appear to us that this procedure is justifiable only in the newborn period in cases of severe deformity, as an aid to skin closure, and in very rare circumstances in older children.

Complications of Orthopedic Management

Failure of attempted arthrodesis is a common occurrence in the management of patients with myelomeningocele. Osteomyelitis as a complication of bone operations on the feet occurred in roughly 6.6 percent of the patients in the series of Hayes and associates.[5] Kilfoyle and associates,[27] on the other hand, reported no incidence of infection in 19 spinal stabilization procedures.

Impaired sensation with resulting trophic ulceration is a common complication in the management of these patients and is commented on by numerous observers. Carr,[4] in an earlier series, stated that the incidence over a period of some years was 50 percent in patients who had sensory loss. The common sites were the posterolateral aspect of the heel, the outer side of the foot, the dorsum of the toes, and the buttocks. In older series, 50 percent of patients in whom such ulcers developed on the feet ultimately had to have amputation. Hayes, Gross and Dow,[5] in reviewing their 100 cases, found that amputation below the knee or more distally had occurred in 13 cases. The causes included infection (most commonly), severe deformity, fractures, and Charcot joint. In 24 of their patients, trophic ulcers significant enough to require operative treatment occurred. Bluestone and Deaver[35] in their experiences with 45 children reported decubitus ulcers in 19 patients. In six cases the lesions were regarded as serious. Numerous observers stress the need for frequent examination of the skin for pressure areas.

Neuropathic arthropathy was found by Hayes and associates[5] in eight of 100 patients—in the ankle joint in six cases, in the talonavicular region in one and the knee in one. Carr[4] said that he had only one such case, with the ankle and tarsal joints affected, in a series of 100.

Fractures and epiphyseal separations are a common complication, occurring with apparently minimal trauma, in many of these children.[23,36-40] Cases have been reported by Gillies and Hartung[36] in which the callus was so exuberant that it was mistaken for sarcoma on the basis of x-ray visualization and biopsy. These fractures are often virtually painless and the only presenting signs are swelling and heat. In 1965, Freehafer and Mast[41] reported their experience with lower-extremity fractures in patients with spinal cord injury. There were 46 fractures in 23 such patients. Based on this experience, the authors advocated treatment with pillow splints and well-padded plaster casts. For hip fractures they advocated positioning of the hip only, without internal fixation.

Habilitation

With regard to habilitation of these patients, there was for many years unjustified pessimism. This was reinforced by Jaeger's[42] article in 1953, in which he stated that in studying 68 case histories he was able to find no survivors over the age of 10; he attributed these early deaths to urologic complications. It has become increasingly apparent, however, that with vigorous neurosurgical, urologic and orthopedic management many of these patients can become self-sufficient. As early as 1959, Norton and Foley[43] in a study of paraplegia in children found that of 26 patients, 19 of whom were over 18 years of age, 13 were self-supporting. This group included postnatal as well as congenital paraplegics. Independence, once it is achieved by these young paraplegics, appears to be permanent. Bluestone and Deaver,[35] Norton and Foley,[43] and Sharrard[44] have all made the point that remarkable degrees of self-sufficiency have been achieved by many of these children. Sharrard contends that more than 80 percent can lead an independent existence, although the average number of orthopedic procedures required in the lower limb was between six and eight in his series. The capacity of paraplegics for sustained ambulation is limited by the high energy expenditure required. Gordon and Vanderwalde,[45] in a study of this problem, found that the energy ceiling is approximately five to six times the basal metabolic rate; this value approaches the athlete's tolerance for sustained physical activity and is limited in the paraplegic by the decreased absolute capacity for anaerobic work resulting from the small muscle mass of the arms. When the lesion is at low lumbar and sacral levels, bracing can be minimal and the patient should be completely independent in all activities. Employment is limited only by moderate deficiencies in the activities of ambulation and elevation in such persons. In those with upper lumbar level lesions, only about half will remain functionally ambulatory, and wheelchair independence is a more realistic goal.[46-50]

Efforts directed toward the goals of a straight spine, straight legs and feet, mobile hips, and, if possible, the development of a pull-to or swing-to gait should be started as soon after birth as possible. Corrective measures for knee, foot, and ankle deformities should not be deferred. Soft-tissue releases may be indicated in certain children under the age of one year. In addition, abduction casting and splinting in an effort to avoid the complication of paralytic dislocation of the hip may be indicated during the first year of life, although this problem remains unresolved at the present. Tendon transfers and neurectomies to correct imbalance are indicated throughout childhood; rotational osteotomy, triple arthrodesis, and spinal fusion may be necessary in some older children.

Upper-extremity strengthening by having the patient walk on his hands while someone holds his legs "wheelbarrow" fashion, and chin-ups should be begun as early as cooperation can be obtained from the child. There are no data of significance as to how early in life these children can be trained in walking. We favor the assumption of the upright posture, either sitting or standing, between six and twelve months of age; fitting for such braces as are indicated; and gait training in parallel bars, proceeding to crutches between one and two years of age. With quadriceps weakness, long leg braces will be required. Results of lesions at the third lumbar level and below, with weakness below the knee only, can be managed with short leg braces if deformity is avoided. Rotational instability of the hip can be a problem in some patients who have adequate quadriceps strength to obviate the need for long leg braces. We have had success with the use of cable twisters attached to the shoes, along with "shoe-horn" laminated plastic inserts for flail feet in some patients, thus avoiding the need for double-upright long leg braces with pelvic band and drop-lock hips. Some loss of stability is conceded in exchange for the much lighter and more easily donned apparatus. Even with lesions at levels as high as the twelfth thoracic segment, we favor such bracing as appears necessary and gait training in early childhood,

recognizing that many of these children will not remain ambulatory as they get older, particularly if they become obese, and that they may find that their high energy expenditures and slow forward progression militate against continued effective ambulation. It is our feeling that bone structure may thus benefit, and perhaps minimize, osteoporosis of disuse and subsequent incidence of fractures. This is another area in which no definitive data have been published.

Summary

The orthopedic and habilitative aspects of the management of patients with spina bifida is complex, involving deformities of the spine, pelvis, hips and lower extremities, and optimal treatment remains undefined in many areas. It is clear, however, that previous pessimism regarding the ultimate self-sufficiency of many of these patients is not justified at present. Early and vigorous orthopedic management can make a definite contribution to the long-term welfare of these unfortunate children.

Addendum

In the time between the presentation of these rounds and their publication, a number of papers and several texts have appeared which have made significant contributions to the orthopedic management and habilitation of myelomeningocele. The American Academy of Orthopaedic Surgeons has published a Symposium on Myelomeningocele,[51] as have several other groups.[52,53] In addition Menelaus[54] has written an excellent monograph. Other significant contributions from the orthopedic literature are summarized here.

Sharrard, with a large experience in England,[55] has recently reviewed his criteria for surgical operation of the hip, knee, foot and spine. He remains enthusiastic about the treatment of children with myelomeningocele, while tempering some of his earlier enthusiasm for immediate closure of spinal defects in all children.

Eighteen patients from a crippled children's hospital (cared for between 1943 and 1959) were followed-up to evaluate functional ability at ages 17 to 31 years.[56] There were 17 survivors, of whom 12 were termed "competitive" (defined as being independent in activities of daily living and either self-supporting or attending school with good prospect of becoming self-supporting). Four were dependent but not institutionalized and one was confined to a wheelchair in an institution at age 26 years. Fifteen of the 18 had required surgical procedures to eliminate pressure sores; a total of 107 orthopedic or skin-related surgical procedures had been required among the 18 patients. There was no clear relationship between either the level of paralysis or the intelligence quotient and competitive ability.

The subject of paralytic vertical talus has received increasing attention because it occurs in children with functioning fifth lumbar level nerve roots, a level which permits good ultimate ambulatory capacity. Walker and Cheong-Leen[57] opened a discussion on its treatment, at the 1973 spring meeting of the British Orthopaedic Association, which is informative to those who must deal with this problem. It indicates a considerable diversity of opinion as to optimal management as well as pathogenesis of this deformity.

Duckworth and Smith[58] agree with those who believe that imbalance between the evertors and the invertors of the foot is the cause of this deformity, with the peronei acting strongly with the ankle and toe dorsiflexors to overpull the tibialis posterior and the intrinsic foot musculature. They compared the results of release procedures alone with those of combined release and transfer of the peroneus brevis to the tibialis posterior and the tibialis anterior to the neck of the talus, and concluded that there is at present no consistently satisfactory operation when neuromuscular imbalance exists. Two out of three patients were improved, however.

Kopits[59] has extensively reviewed orthopedic problems and habilitation and suggests decancellation of the talus and cuboid as originally practiced by Verebélyi and Ogston for the management of rigid paralytic clubfoot.

It has been shown by Hay and Walker[60] that plantar pressures in the feet of children with myelomeningocele are substantially higher than in the feet of age- and sex-matched normal controls. They attribute this in part to the smaller size of the feet in spina bifida, and also postulate that feet in which a previous posterior release has been done are in a condition which they term a "flail deformity," wherein the hindfoot receives excessive loading while the forefoot lies limply and escapes its share of the load.

In the management of paralytic dislocation of the hip, London and Nichols[61] reported superior results from transferring the adductor origin from the pubic tubercle to the ischial tuberosity in combination with a modified Mustard iliopsoas trans-

fer in the third, fourth and fifth lumbar levels in myelodysplasia. They compared the results of this procedure to those obtained following Sharrard's posterolateral iliopsoas transfer and came to the conclusion that reduction of the dislocation and a level pelvis were more easily maintained due to improved muscle balance about the hip if the adductor origin was also transferred.

The indications for iliopsoas transfer were questioned by Carroll,[62] who feels that this transfer weakens hip flexion but is unlikely to provide abductor or extensor power and should not be done in children with high paraplegia or lumbar kyphosis who are unlikely to walk.

Barden, Meyer and Stelling[63] followed 29 survivors of a group originally consisting of 63 severely involved myelodysplastic patients who had been given care from 1928 to 1951 at a Shriners hospital. All had been ambulatory while in the hospital as children, but only two of nine with twelfth thoracic to second lumbar level function were still walking, whereas 19 of 20 with function at the third lumbar level had remained ambulatory. Of considerable interest is the observation that the final position of the hips did not correlate with the ultimate ambulatory status; seven of these 20 patients were ambulatory in spite of persistent hip dislocations. About half of the entire group had scoliosis, and a third of the survivors were self-supporting in full-time employment.

In a small series of young patients, McKibbin[64] has been able to use a specially designed abduction splint effectively to maintain reduction of paralytic dislocation of the hip. He suggests that this may be a useful adjunct to treatment in the first year of life in those patients with preserved flexor and adductor groups (second and third lumbar levels) until the prognosis for the individual has been assessed.

Sriram, Bobechko and Hall[65] reviewed data on 33 patients who had been treated for spinal deformities by operation and who had been reevaluated from a year to 11 years later. Twenty-nine had had posterior spinal fusion, and 26 of these had had Harrington instrumentation as well. Infections and pseudarthroses were common as well as difficult complications to manage, and good results were obtained in only half the patients. They advocate two-stage fusion if the skin is badly scarred or if a residual sac requires excision. This article underscores one of several remaining problem areas in the management of myelomeningocele.

Menelaus[66] has joined those who advocate osteotomy-resection of kyphosis at the time of posterior closure, which is facilitated by the excision of protruding bone. He states this can be done up to the age of four years, and further states that fusion was obtained in all cases treated in this way.

An improved shortleg brace, made of plastazote-lined polypropylene, for children with third to fifth lumbar level paraplegia has been successfully used by Lindseth and Glancy[67] in 47 patients. The authors believe that this device brought about considerable improvement in the gaits of nearly all the children and they further state that it represents a major advancement in bracing at this neurological level. Carroll[68] has recently reviewed current concepts in bracing and the use of carts and standing devices.

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MYELOMENINGOCELE—PART II

Ophthalmologic Problems

ERNEST K. GOODNER, MD, *San Francisco*

DEVELOPMENTAL abnormalities of the eye may occur in association with defects in the formation of the midline portions of the cranium and spinal column. These ocular anomalies are severe, rare and generally not susceptible to treatment or repair. Fortunately, the majority of children with spina bifida and related conditions have normal eyes and visual development.

The ocular abnormalities that occur in association with malformations of the cranium and vertebral column are produced generally in one of two ways: (1) Defects in ocular function may result from the direct effect of maldevelopment in the cranium or vertebrae on underlying neural components of the extraocular visual system (for ex-

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Part II of an article in six parts.

From the Department of Ophthalmology, University of California, San Francisco.

Reprint requests to: E. K. Goodner, MD, Department of Ophthalmology, University of California, San Francisco, San Francisco, CA 94143.

ample, a defect in the cervical vertebrae and cord may produce Horner's syndrome); or (2) embryologic disturbances may occur concurrently in several separate structures, resulting in, for example, spina bifida and absent ganglion cells in the retina.

Cranium bifidum in a few of its various forms may produce associated eye problems. Anterior defects which result in nasofrontal encephalomeningocele usually produce lateral displacement of the orbits, and varying degrees of hypertelorism result. This abnormally increased distance between the eyes may interfere with convergence and also makes the fitting of glasses very difficult. Rarely, an orbital encephalomeningocele may be encountered, presenting as a mass in the nasal side of the orbit and causing exophthalmos and lateral displacement of the globe. Neurofibromatosis may produce bony defects anywhere, including the posterior orbit, and may result in a posterior orbital encephalocele. Posterior cranial defects, especially those in the occipital region, may cause defects in the optic radiations or the occipital cortex, producing some degree of cortical blindness. The latter condition may be difficult to diagnose in an infant but should be suspected when the usual responses to visual stimuli are absent in the presence of anatomically normal eyes and normal pupillary light reflexes.

The Arnold-Chiari malformation is frequently associated with spina bifida and hydrocephalus. This condition affects the hindbrain, cerebellum, and upper cervical cord and produces nystagmus and diplopia.[1] Spina bifida of the cervical region may produce a partial Horner's syndrome, but this is probably rare except in the presence of severe intrinsic damage to the cord. Defects in other regions of the vertebral column cannot directly affect ocular function.

Severe ocular developmental malformations are rare but do occur and include anophthalmos (absence of one or both eyes), microphthalmos, and colobomas of the iris, lens and choroid. A coloboma is due to partial or complete failure of closure of the fetal fissure in the development of the eye and is seen clinically as a notch or gap in the inferior iris, choroid or even the inferior edge of the disk. Aplasia of retinal ganglion cells, absence of the macula, atrophy of the optic nerve and, rarely, absent optic nerves have been reported.[2-4]

Since the majority of children with spina bifida have normal ocular development, they are therefore subject to the normal incidence of strabismus and refractive errors. Eye examination, including an estimate of the visual acuity and an evaluation of extraocular muscle function and ocular alignment, must be done if amblyopia is to be prevented or treated effectively. Considering the severity of many of these children's other problems, they should have the benefit of the best vision of which they are capable. The problem of locomotion is often severe, and normal school attendance becomes difficult if not impossible. As a result they will not participate in the school visual screening program and hence do need individual eye examinations. In the absence of gross ocular abnormalities easily detected in the newborn or in early infancy, an eye examination should be done in the preschool period between the ages of three and five years. At this age, a certain degree of cooperation is present, most of the important causes of early visual deficiency will have appeared, and in most cases adequate time to treat or prevent the development of amblyopia remains.

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Myelomeningocele—Part III

Urologic Considerations

EMIL A. TANAGHO, MD, M Ch, *San Francisco*

Myelomeningocele is one of the most common congenital anomalies. Fortunately it is also most amenable to treatment.[1,2] Today many of the

Part III of an article in six parts.

From the Division of Urology, University of California, San Francisco.

Reprint requests to: E. A. Tanagho, MD, Division of Urology, Moffitt Hospital—#478, University of California, San Francisco, San Francisco, CA 94143.

children with myelomeningocele may be promised a longer life than was formerly possible.

Occasionally, a patient with myelomeningocele is born with already established urologic changes, but most often the urinary system is intact at the time of birth.[3] However, a recent study shows that by age four years about 75 percent of the afflicted children have urinary tract infection, 100 percent have abnormal cystograms, 25 percent have reflux, and 30 percent have abnormal excretory urograms.[4]

Their status of urinary incontinence varies. Only 3 percent of them have normal control, mainly patients with lumbosacral lesions.[5] Urologic complications are very common in these patients.[6-13]

The Urologist's Responsibility

As a result of our better understanding and treatment of myelomeningocele, the number of children with this problem is growing. The urologist's first task is to establish the status of the urinary tract as soon as the patient is seen. Urinalysis and intravenous pyelograms (IVP) should be obtained and serum creatinine levels determined.

If the patient is seen right after birth and immediate closure of the defect is contemplated, it is always preferable to obtain an IVP before neurological correction. Not infrequently, as a result of neurosurgery, the patient goes through a phase comparable to traumatic spinal shock, with acute retention and overflow of urine. It is therefore imperative that the bladder be decompressed or emptied regularly. (Ignoring this possibility and allowing the bladder to overdistend for an appreciable length of time might lead to permanent myogenic damage endangering future bladder rehabilitation, even if the neurogenic defect is minimal. It would be tragic to lose a bladder from myogenic damage when the neurogenic defect is insignificant.) In girls, an indwelling catheter should be kept in for a few days and subsequent testing should be performed. In boys, regular 3-hourly Credé emptying is advisable until the bladder resumes its activity and the patients start to void spontaneously.

If results of diagnostic studies are normal the patient should be examined every three months for urinary tract infection and for evaluation of residual urine and should also undergo IVP studies at intervals of six months to a year. If the IVP is normal there is no need for cystographic studies, but with any change in the IVP, voiding cystography is indicated in order to evaluate the competency of the ureterovesical junction.

Urologic follow-up and care of patients with myelomeningocele must be life-long. No matter how well balanced their system, these patients should be checked regularly and carefully by a urologist.

Basic Urologic Problems

Urinary infection, urinary incontinence, and back pressure on the upper urinary tract are the three basic problems confronting urologists in the management of myelomeningocele.

Urinary Tract Infection

Infection of the urinary tract is a very common complication, due mainly to the constantly encountered residual urine. It is less common in boys than in girls because the urethra is shorter in girls, and the perineum more often infected. The complication is made worse by fecal incontinence. Symptomatic urinary tract infection should be treated according to sensitivity. Most of the time the infection can be eradicated successfully and suppressive medication is used to prevent its recurrence.

In asymptomatic patients whose infection cannot be cleared it is useless to pursue its elimination; no suppressive medication should be used.

The less the amount of residual urine, the better the chances of clearing the infection; at least twice daily attempts should be made to empty the bladder almost completely, using Credé's or Valsalva's maneuver as indicated. In the absence of reflux, bladder infection is relatively harmless.

Urinary Incontinence

In most cases of myelomeningocele, bladder and sphincter function are disturbed. The degree of bladder involvement depends on the level of the lesion. In cervical or upper thoracic lesions, bladder involvement may be minimal. However, this type of lesion is relatively rare. In low thoracic and thoracolumbar lesions, bladder involvement is partial and a certain degree of rehabilitation is almost always possible. The disorder at this level is usually a partial upper motor neuron lesion with intact spinal reflex. In low lumbar and lumbosacral lesions the bladder is generally severely involved. These lesions implicate lower motor

neuron changes and are associated with a flaccid sphincter and a passive type of incontinence. Again, this lesion is rarely total: On its degree of severity depend the future chances of rehabilitating the bladder. Patients with this type of lesion, however, have the highest incidence of persistent urinary incontinence. They also carry appreciable residual urine in spite of minimal outflow resistance. They are often amenable to Credé emptying of the bladder; if done regularly this technique is instrumental in making infection less likely to occur and more easily manageable when present; moreover, it improves the state of continence. These patients usually start to leak urine after accumulating a certain amount in the bladder. If the bladder is completely empty they stay almost dry until the same volume of urine has once more accumulated. If nearly complete emptying is allowed several times a day, a reasonable degree of continence can be maintained. In these cases, incontinence is a relative protection against the possibility of rapid deterioration of the urinary bladder and the upper urinary tract. This is in contrast to the situation in patients with pseudocontrol due to a relatively higher lesion, with partial spasticity of the pelvic floor and of the external sphincter, which leads to smaller functional capacity and higher intravesical pressures. The upper urinary tract of the latter patients deteriorates more rapidly.

Back Pressure on the Kidney

Two factors are basic in the development of back pressure on the kidney: (a) substantial residual urine, resulting in trigonal hypertrophy and stretching, and (b) vesicoureteral reflux resulting from decompensation of the ureteral orifices. Conversely, in the absence of any appreciable residual urine in a smooth bladder, and in the absence of reflux, the upper urinary tract is usually well preserved.

The goal of the urologic care is the prevention of damage to the upper urinary tract. Regular examination by IVP, and cystogram when indicated, are essential to detect the early signs of incipient ureteral dilatation and back pressure on the kidney.

Trigonal hypertrophy, commonly seen in these patients, increases the resistance to flow in the intravesical ureter; if compounded by any degree of trigonal stretching resulting from residual urine, it exacerbates the functional obstruction of the intravesical ureter and leads to progressive back pressure on the kidney. Relieving trigonal stretching by eliminating the residual urine with continuous catheter drainage frequently leads to pronounced diminution of the degree of dilatation of the upper urinary tract.

As long as the ureterovesical junction maintains its competence, the degree of dilatation of the upper urinary tract is limited, but if reflux develops, rapid decompensation and deterioration of the upper tract usually follow. Infection gains an easy access and pyelonephritis sets off complications in what was previously a benign lower urinary tract infection. The hydrodynamic effect of the reflux, compounded by the pyelonephritic scarring due to the ascending infection, further accelerates the loss of renal parenchyma and the deterioration of kidney function.

It is usual for most of the patients to have a relatively stable course as regards the upper urinary tract until a sudden dramatic change occurs (Figures 1 and 2). The possibility of this change dictates continuous checking at short intervals with IVP and cystogram. No more than one year should be allowed to pass without repeating these studies.

Once reflux develops, there is rarely much hope of maintaining the integrity of the upper urinary tract. Any amount of residual urine in the presence of reflux becomes significant. The Credé maneuver can no longer be used since it aggravates the degree of reflux and increases the pressure on the kidneys; at this point it is absolutely contraindicated. Constant catheter drainage is helpful temporarily but is not acceptable as a lifelong policy (Figure 2C).

Regular intermittent catheterization in the presence of reflux is not satisfactory either. In selected cases, ureteral reimplantation, followed by intermittent catheterization, may preserve the integrity of the upper urinary tract and partially improve the incontinence.

If progressive upper urinary tract damage develops because of reflux, supravesical urinary diversion is, as a rule, the treatment of choice. This will also correct uncontrolled incontinence. In cases of moderately dilated ureters, ureterostomy, using a single stoma for both ureters on either the right or the left of the midline, can usually be accomplished. One should not, however, wait until there is appreciable dilatation, since this usually means increased damage to the upper urinary tract. If diversion is indicated, ileal or colonic loop

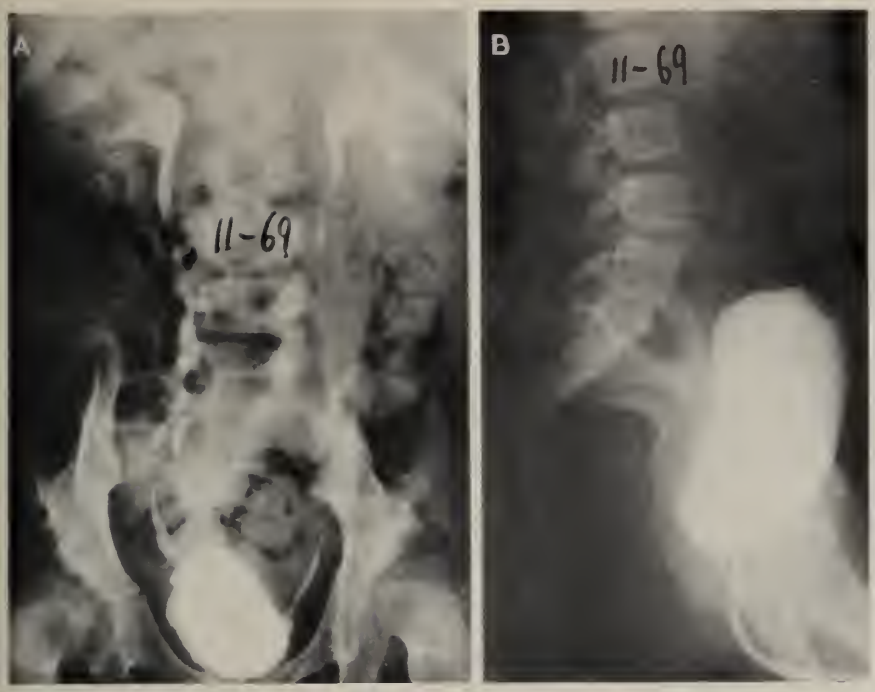

Figure 1.—The patient is a 6½-year-old child with myelomeningocele. **A**, IVP. Well-functioning upper urinary tract bilaterally, with minimal dilatation of right lower ureter. **B**, Cystogram. No reflux, but mild trabeculation and bladder thickening.

Figure 2.—Same patient as in Figure 1, 13 months later. **A**, IVP, revealing notable impairment of kidney function with bilateral hydroureteronephrosis, more marked on left side. **B**, Cystogram, revealing left vesicourethral reflux. **C**, IVP after three weeks of constant catheter drainage, showing distinct improvement in the degree of hydroureteronephrosis.

diversion is the best procedure. For the last four years we have been doing colonic loop diversion with antireflux ureterocolonic anastomosis to prevent any ascending infection and also to allow for free drainage (Figure 3). In our opinion, this procedure leads to satisfactory long-term results.

After the diversion operation the patient still has to be followed closely, for no diversion procedure is immune from future complications, especially from obstruction to the loop or at the site of ureteral anastomosis. Infection and stone formation are also common. We feel that all these

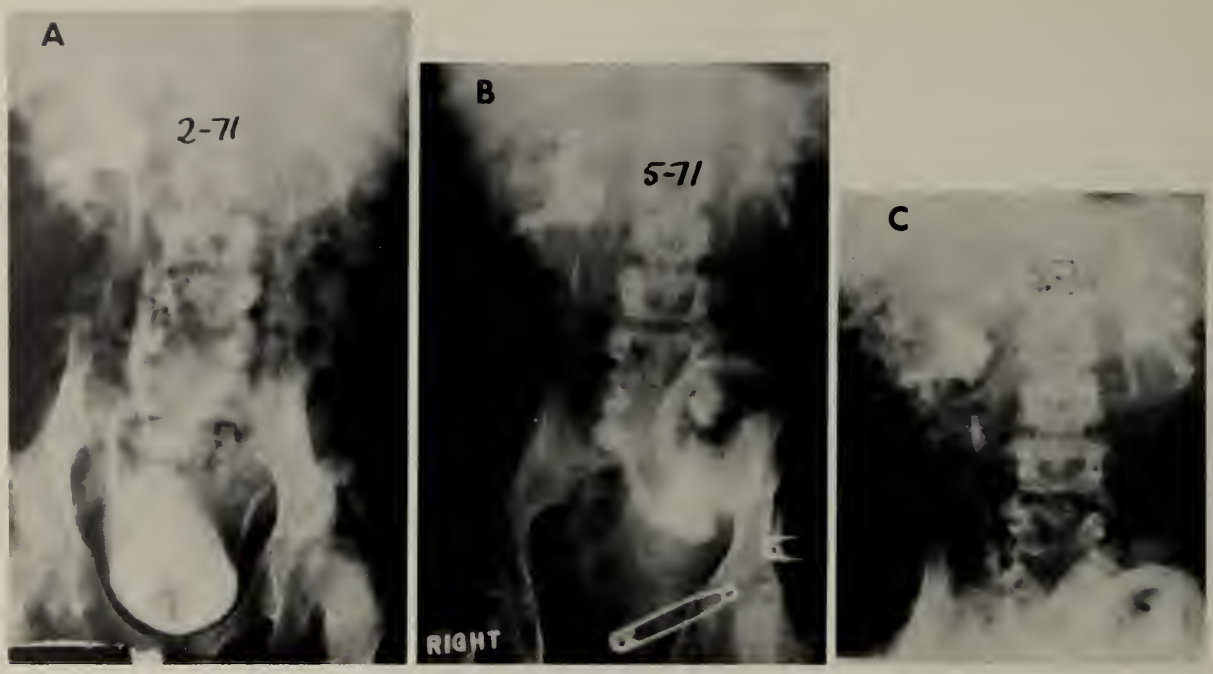

Figure 3.—Same patient. **A,** IVP before diversion and after three weeks of constant catheter drainage. **B,** IVP three months after colonic loop diversion with antireflux ureterocolonic anastomosis. Further improvement in the hydroureteronephrosis. (The loopogram showed reflux in the reimplanted ureters.) **C,** One year after colonic diversion. Persisting improvement in kidney function.

postoperative complications are much less apt to occur in colonic loop than in ileal loop diversion.

Discussion

Some physicians advocate early diversion (at age two years), before any change in the upper urinary tract appears, on the premise that in such a case future deterioration is substantially reduced. I feel that as long as the integrity of the upper urinary tract is intact, it is better to wait, in the hope that some degree of bladder rehabilitation with reasonable control will ensue. Incontinence in males is easier to handle by external appliance, and I am therefore reluctant to use diversion techniques for incontinence alone in males. The situation is different in female patients, as there is no efficient device for the control of urine, and occasionally incontinence is so severe that diversion has to be performed. Chances for complete control are very low—3 to 5 percent. Partial and reasonably good control can usually be achieved in a higher proportion of patients.

Urinary tract failure is the main cause of death following successful neurosurgical repair of myelomeningocele. Every effort should be made to prevent any kidney damage from pyelonephritic scarring and back-pressure effect. Close follow-up is essential. Conservative management and control of infection are all that is needed as long as the upper urinary tract is normal. The moment any change in the upper urinary tract appears, aggressive measures for protection of the tract should be taken.

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Refer to: Prince B: Myelomeningocele—Part IV: Psychosocial problems and social work interventions, *In* Myelomeningocele—A symposium. West J Med 121:297-298, Oct 1974

MYELOMENINGOCELE—PART IV

Psychosocial Problems and Social Work Interventions

BARBARA PRINCE, MSW, *San Francisco*

THE PSYCHOSOCIAL PROBLEMS resulting from a diagnosis of spina bifida can be enormous for the child and his or her family and have the potential for interfering greatly with a reasonably normal life for both. In most cases stresses are directly related to the multiplicity and severity of the medical problems with which each child is affected. Other contributors to this symposium emphasize the need for immediate involvement with the family by a team of experts. I shall discuss the problems that arise after the initial period of trauma and continue thereafter and the social work interventions that enable the child and family to cope with the problems.

The following psychosocial problems may be anticipated:

- Financial strain on the family budget
- Physical and emotional strain on the chief caretaker, usually the mother
- Social isolation of parents and child
- Difficult decisions and feelings related to family planning
- Anxiety accompanying a variety of ongoing medical and surgical procedures
- Inability of parents to allow child maximal independence
- Emotional trauma to parents and child when the child must be placed outside the home
- Problems due to bowel and bladder incontinence, particularly when the child is away from home
- Anxieties about sexual functioning
- Child's poor self-image and concern about physical appearance
- Generalized worry about the future

Social work services fall into three major areas: referral to and follow-up with community agencies, casework with child and family, and communication.

Medical costs can be enormous and may continue for many years, so parents need information as to what financial resources are available, and they may need emotional and concrete assistance in doing what is required to obtain financial support. A public health nurse is a valuable asset to the family and the clinic team in providing continuity of care as well as teaching and supervising the care given by the mother. For instance, parents do not always understand the techniques or importance of emptying a child's bladder. Most children with spina bifida attend schools for the orthopedically handicapped and the social worker acts as liaison with school staffs when necessary. A referral to a sheltered workshop or the department of rehabilitation is indicated for some older teenagers. Occasionally there is a need for parents to have more intensive counseling than can be given by the social worker during clinic visits and a referral is made for family or marriage counseling. If a child is placed outside the home, the child welfare services worker and caretaker will need information about spina bifida and the psychosocial problems the child has both manifested and encountered. Joe, 14, was placed in a residential treatment center because the family could not cope with his disabilities, particularly incontinence. The staff at the center, through lack of information, reacted to him much as his family had and he began to repeat unacceptable behavior until the social worker provided the staff with an understanding of Joe's problems.

During clinic visits, the social worker provides casework to parents and child. She evaluates the emotional, physical and financial ability of the parents to carry out recommendations and to provide necessary care at any given time. Alice's family was shaky but gave her adequate care until she was nine, when it became obvious that conflicts within the family, compounded by Alice's medical problems, made it impossible for the parents to care for her adequately any longer. Casework enabled parents to make a decision to place their child in a foster home and Alice began to adjust to the change.

Part IV of an article in six parts.

From the Department of Social Work, University of California, San Francisco.

Reprint requests to: Barbara Prince, MSW, Department of Social Work, University of California, San Francisco, San Francisco, CA 94143.

Parents require ongoing supportive casework to cope with long-term responsibility and care, to make decisions repeatedly about hospitalization and procedures. They need encouragement to maintain social activities away from the child and to ask for and find resources for relief from 24-hour care. Fifteen-year-old Ted had massive orthopedic involvement. His mother was a single parent who until his first clinic visit had hardly left the house for several years. Parents are greatly in need of genetic counseling to resolve feelings of guilt which are often present and to fully understand the risk of recurrence of spina bifida in future children.

The social worker may have to emphasize over and over the value in a child's being as independent as possible. Two years went by before ten-year-old Mary's mother reached a point where she could allow Mary to change her own diapers. The older child who presents a physically normal appearance but lacks bowel and bladder control needs not only adequate devices and instruction in self-care but help in accepting and living with this problem. The focus of casework is on developing an optimal self-image. It was only when Jane, 13, began to feel some sense of self-worth that she was ready to keep herself clean enough to eliminate the odor of urine which had made her open to ridicule and social isolation.

Psychosexual counseling is crucial for teenagers and parents. The older the child, the more specific the information he or she must be given. To provide this type of counseling the social worker has to be well informed and comfortable in dealing with the subject. Tom, 18, who wore a catheter, was starting college without ever having dated and had decided he would never marry. In one clinic visit with the social worker he began to see the possibilities open to him for achieving an adequate sexual relationship and to approach the subject of his psychosexual functioning from a different viewpoint.

The social worker is an important link in the chain of communication between child and family and clinic team. She informs the team of psychosocial problems which interfere with treatment or make it unrealistic to expect that recommendations will be carried out. Paul was confined to a wheelchair and was obese. The team repeatedly urged his mother to put him on a diet (which she did not do) until the social worker pointed out that the whole family was obese and not apt to change their eating habits. The social worker is sometimes the only member of the team who knows all the questions the child or family has, so she makes sure that questions are asked and answers are understood. She is usually the liaison who keeps communication open between clinic team and community agencies. The importance of her role in maintaining the flow of communication in all directions cannot be overemphasized.

Refer to: Pevehouse BC: Myelomeningocele—Part V: Neurosurgical aspects, *In* Myelomeningocele—A symposium. West J Med 121:298-300, Oct 1974

Myelomeningocele—Part V

Neurosurgical Aspects

BYRON C. PEVEHOUSE, MD, *San Francisco*

The problems of myelomeningocele and meningocele are those of spinal dysraphism. These are not isolated defects, but rather conditions that involve the entire motor system. The ventricles and the circulation of the spinal fluid, as well as the spinal cord and its coverings, are involved. The meningocele that one observes is actually an outline of the meninges protruding through a bony defect; it has spinal fluid in it and occasionally it will also have some fat but it has no nerve tissue, this absence being basic to the definition of a meningocele—that is, the cord and the nerve roots are intact and are not involved in the defect.

A more serious lesion, that of meningomyelocele, or what we now prefer to call myelomeningocele, putting the cord part first, always involves the spinal cord as a part of the defect. There may be displacement of the cord, duplication of the cord, or separation of it, often in the lumbosacral region, and there will be tethering of roots in the dome of the defect with a consequent neurological deficit. We have found the ratio of myelomeningocele to simple meningocele to be about eight to one. There are also more rare and complicated forms of rachischisis in which the cord is displaced into

Part V of an article in six parts.

From the Department of Neurological Surgery, University of California, San Francisco.

Reprint requests to: B. C. Pevehouse, MD, Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA 94143.

the defect or split, and in which there is dilatation of the central canal. These lesions all have an individuality of their own. No two defects look exactly the same; they come in all sizes, shapes, and locations.

The Arnold-Chiari malformation is very similar. It is a part of the whole problem of spina bifida in that there is deformity of the ventricles, the midbrain, and the posterior structures of the cerebellum, resulting in displacement of the cerebellar tonsils downward into the cervical canal and compression of the cord, which in turn causes obstruction of spinal fluid flow through the area. Displacement of the medulla causes disturbances of the lower cranial nerves, and any child with this deformity may have trouble breathing, or stridor when crying. Such a child is in danger of having respiratory arrest.

Other lesions that occur may be occult but are often serious. Lipomas involving the cord or roots may be heralded only by a small tuft of hair at the base of the lumbar spine or a dimple which in some instances will be a source of repeated meningitis, and not until the second or third episode in the same child—following which there may be serious deficits as a result of the meningitis—does the reason become apparent.

It should again be emphasized how many lesions are in the lumbosacral area. In our series of 295 lesions there were only seven above the level of the first lumbar vertebra. They may, however, occur anywhere along the neural tube. The defect has its origin about the thirtieth to forty-fifth day of gestation with failure of closure of the neural tube. It may occur at the very rostral end and involve the cribriform plate and the base of the brain, or it may be anywhere as far caudally as the sacrum.

Even in what may appear to be a simple meningocele, there may be some neurological deficit indicating that the lesion is in reality a myelomeningocele. As the child grows a little older, some lesions may develop into a cicatrix following a granular repair within a lesion. One may see abnormal hair in some. Another feature of the myelomeningocele sac is the abnormal skin around the periphery with a very attenuated arachnoid in the center, directly beneath which lies spinal fluid. This is the area from which leakage takes place, and leakage is the great danger since it may lead to retrograde infection and meningitis.

Some of the lesions of the cranium can also cause ventricular displacement in which there may be a connection between the third ventricle and the two lateral ventricles, often accompanied by distortion of the cerebellum and occasionally with involvement of some of the venous sinuses that are part of the tentorium. As mentioned above, however, the typical defect is lumbosacral and is accompanied by a neurological defect. There is usually both bowel and bladder disturbance. In many of these babies rectal prolapse develops very rapidly, because of sphincter incompetence, and the prolapsed segment may feed out 15, 20, or 25 cm of mucosa. This prolapsed segment has to be protected during the first few weeks in many of the children, and to do so the buttocks are often taped together.

In our efforts to preserve whatever neurological function is present, we are concerned with the neural tissue in the center of the sac. The neural elements are usually extruded and must be covered in order to prevent infection, by constructing a layer of meninges which will prevent spinal fluid leak and allow some sort of satisfactory skin closure. These children often have problems with leakage of spinal fluid because 80 to 90 percent of them have hydrocephalus resulting from the dysraphism itself. Some of them have communicating hydrocephalus, some have aqueductal blocks, or in the case of the Arnold-Chiari malformation there may be a block of the foramen magnum. In the repair of these lesions it is important to identify the neural elements, although the cord may end in the defect, with no continuation; such a child is totally paraplegic. In this event it is important to tailor the neural elements properly to prevent tethering of the cord as the child grows, and also to effect a proper dural closure to keep the spinal fluid system intact. Sutures in the skin are avoided whenever possible unless there is tension on the grafts. Mere removal of these lesions greatly simplifies nursing care. There are children who have gone as long as three years with large lesions, but from a technical standpoint 98 percent of all lesions of this sort can be closed. It has not been clearly demonstrated that this makes any great difference neurologically, but it is our belief that by preventing complicating meningitis, and also by trying to preserve all the remaining neural elements that are present, there may be some sensory reinnervation to a level or two lower at some later time. There are a number of patients who have not been operated upon and have survived; in this type of series one finds that such children had small le-

sions which spontaneously granulated in. Thus they did not require operation and still survived. However, nearly all children not operated upon will die. If the primary physician, or other personnel involved, advises against repair of the lesions, then there must be some method of euthanasia so that such children do not constitute a burden to either the parents or the state.

After the spinal lesion has been closed and the problems of meningitis are gone, the neurosurgical problem that then remains is control of the hydrocephalus which usually develops. The onset of hydrocephalus in the newborn is apparent either at birth or within the first month or so. This is important for the primary physician to realize. The head should be measured, the fontanelle should be inspected and palpated to determine tenseness, and the findings should be recorded so that a week or two weeks later it can be determined whether there has been a change. Many times a baby is seen at one or two months of age and there is a question as to whether hydrocephalus exists or not, but there is no previous head circumference measurement available for comparison, even though the ventricles are in fact beginning to dilate. As far as the remainder of the neural tube is concerned, there may be associated defects anywhere which can cause hydrocephalus; they can be at the aqueduct, as is often the case in the Arnold-Chiari malformation, or in the posterior fossa. Occasionally, failure of development of the proper system of arachnoidal villi to return spinal fluid to the blood circulation is postulated. A block anywhere in the circulation of cerebrospinal fluid will produce hydrocephalus, and anything which obstructs the one-way flow of spinal fluid as it enters the venous system does the same thing although more slowly.

There are many terms, such as communicating hydrocephalus (so called because a dye placed in the ventricular system can be recovered in the spinal fluid), but that does not necessarily mean that there is no obstruction around the base of the system, such as in a postmeningitis situation. Any block, depending on its location, may cause enlargement of the head from increased intracranial pressure. It is obvious that a block of the aqueduct will cause a very rapid ballooning of the ventricles. A block around the base of the system may be partial, so that head growth may be only very slightly increased over normal, and it may take a long time to make the diagnosis that the ventricles are abnormally enlarged.

The present method of treatment is to place a shunt that goes from the ventricular system either to the peritoneum or to the blood stream through the jugular vein, reaching the auricle via the superior vena cava. Several types of shunts are available, some with a palpable reservoir, placed in a bur hole, that provides a little pumping system. When a shunt is made in a child with spina bifida, the meningocele itself in many instances will collapse and make it easier to treat, but there is a converse problem in that if infection is present, it sometimes will get into the system and thereby cause the very complication that it is intended to avoid, namely, infection of the shunt itself, with subsequent obstruction to spinal fluid flow. The decision regarding therapy is a complex problem; each case must be dealt with by first making an accurate evaluation of flow and then trying to see which approach appears best. In many instances a shunt is not the best answer for a child with minimal hydrocephalus. There are many reasons for this, relating of course to the possibility of postoperative infection and also to the effects on the ventricular wall in a marginal hydrocephalus that may already be arrested. Problems often occur in maintaining proper function of shunts, but if we can control the hydrocephalus after the lesion has been repaired, then the real threat to life is urinary tract infection.

Refer to: Cohen P: Myelomeningocele—Part VI: General considerations, *In* Myelomeningocele—A symposium. West J Med 121:300-304, Oct 1974

Myelomeningocele—Part VI

General Considerations

PETER COHEN, MD, *San Francisco*

Spina bifida is a disease entity which includes a group of developmental defects of the spinal column in which there is failure of fusion of vertebral arches, with or without protrusion and dysplasia

Part VI of an article in six parts.

From the Department of Pediatrics, University of California, San Francisco.

Reprint requests to: Peter Cohen, MD, Department of Pediatrics, University of California, San Francisco, San Francisco, CA 94143.

of the spinal cord and its membranes. The term *rachischisis* has been used to refer to this condition, since it indicates a congenital fissure of the spinal column (from the Greek *rachis,* spine, and *schisis,* cleft). A variety of defects can occur in spina bifida:

Spina bifida occulta, in which there is a lack of fusion of vertebral arches without any cystic distension of the meninges, is a common finding in normal children, particularly frequent being fusion defects of the axis and the fifth lumbar, first sacral, and last sacral segments. It may be quite extensive and yet produce no symptoms or signs. The skin over the defect is generally normal but may show a pigmented nevus, a hairy patch, a small lipoma, a dimple, a hemangioma, a scar or, occasionally, a palpable bony defect.

Spina bifida cystica (SBC) may be divided into two categories—(a) meningocele, in which there is lack of fusion of the vertebral arches, with cystic distension of the meninges but absence of myelodysplasia of the spinal cord and absence of neurological signs (the meningeal sac may or may not contain parts of the cord or nerve roots but if it does, they conduct impulses normally), and (b) myelomeningocele, in which there is lack of fusion of the vertebral arches with cystic distension of the meninges, myelodysplasia of the spinal cord, and neurological signs.

The finding of a pure myelomeningocele with a cystic cavity of meninges only, without involvement of the spinal cord or spinal roots, is relatively uncommon. In a study of 306 patients with SBC, Smith[1] could only classify 26 (8.5 percent) as having meningoceles on the basis of operative findings and normal neurological clinical state.

Incidence

Smith[1] reported an incidence of SBC in 1.24 per 1,000 live births, or approximately 1 per 800 live births. It was estimated that about one-third of affected children would reach school age each year; two-thirds of these would have severe neurological disability, and the remainder would have minimal or no disability. With the declining incidence of poliomyelitis, myelomeningocele is now second in importance to cerebral palsy as a cause of chronic locomotor disability in childhood. There is a slightly higher incidence of myelomeningocele in females; out of 371 patients (consecutive cases) reported by Menelaus,[2] 56 percent were girls.

Causative Factors

In a study of 192 families to whom a child with SBC was born, Smith[1] was unable to determine any exogenous factors which could be considered responsible for the development of the defect. He pointed out that in order to affect the spine, any influence on the developing embryo would have to occur in the first few weeks of pregnancy. The neural plate appears first in the late presomite phase, at about 18 days after conception, and the neural tube is completed just after somite formation ceases by the end of the fourth week.

The parents in his study appeared to belong to all levels of society, and no economic or environmental influence could be determined. There was no significant relationship between the development of SBC to birth order or maternal age at the time of birth. Although there was no relationship of the disorder to hydramnios, Smith cited reports in which there was a high incidence of congenital anomalies of the nervous system in hydramniotic pregnancies.

In 15 of 192 families (7.8 percent), there was more than one child in the same family born with SBC. In five other families (2.8 percent), there was a family history of the condition in a close relative.

In a study of families with central nervous system anomalies, Record and McKeown[3] found that 2.8 percent of siblings born after the first malformed child carried a nervous system defect. If no hereditary factor existed, the expected incidence of SBC was 0.45 percent, so there was approximately a six-fold risk compared with that in a normal family; the actual expectancy for a defective family was about 3 percent. The evidence from these and other studies indicates that the risk of having a second affected sibling is fairly high.

In addition to the risk of SBC in subsequent pregnancies, there is a high risk of other congenital anomalies (such as cleft palate, congenital heart disease, or mongolism). In the 192 families reviewed by Smith,[1] in addition to the 20 families with a familial history of SBC, another 15 families had a history of other congenital anomalies.

Clinical Features

Because of the many systems involved, few diseases in medicine require the multiprofessional approach more than SBC. There is not only the defect of the spine and the associated mass on the

TABLE 1.—*Gradings of Disability Related to Spinal Segments in Myelomeningocele Patients (Smith[1])*

Group	*Level of Spinal Lesion*	*Clinical State*
I	Above L_3	Total paraplegia
II	L_4 and below ...	Paralysis of hip extensors and knee flexors. Flail feet. Bladder and rectal incontinence. *But* retention of use of knee extensors and hip flexors and adductors.
III	S_1 and below ...	Weakness of hip extensors and knee flexors. Paralysis of plantar flexors of feet. Weak inversion and eversion of feet. Inability to spread toes or cup soles of feet. Bladder and rectal incontinence. *But* retention of use of knee extensors, hip flexors and adductors, and dorsiflexors of feet; and some use of hip extensors and knee flexors.
IV	S_3 and below ...	Bladder and rectal incontinence. *But* normality of lower limbs.

back, but a high percentage has associated hydrocephalus and also neuromuscular, sensory, and autonomic disturbances, orthopedic problems, bowel and bladder incontinence, and often mental and emotional disturbance. The lumbar and lumbosacral regions of the spine are predominantly affected; 90 percent of the lesions occur below the second lumbar vertebra and 42 percent at the lumbosacral junction.

The muscles of the legs receive their innervation from more than one nerve root and approximately half of the nerve supply to an individual muscle must be lost before paralysis can be detected clinically. Most myelomeningoceles occur in the lumbosacral region and are usually associated with a lower motor neuron paralysis of leg muscles. Depending on the level of the defect, paralysis of muscles may be either flaccid or spastic. Sometimes there are contractures which produce flexion at the hip and extension at the knee. A variety of clubfoot deformities occur. Ankle jerks are usually absent but knee jerks are often present and active.

In a study of 295 patients, Menelaus[2] noted that gross neurological abnormalities were less common when the lesion was high in the spine. Of the three cervical lesions in his group of cases, only one was associated with abnormal neurological signs, and these were minimal. On the other hand, most (approximately 85 percent) of the lumbar and lumbosacral lesions were associated with extensive paralysis. Of 146 consecutive patients with myelomeningocele, 4 percent had minimal or no paralysis in the legs, 20 percent had no innervation below the twelfth thoracic nerve roots, 23 percent had none below the second lumbar nerve roots, and 53 percent had none below the second sacral nerve roots.

There was also a considerably higher mortality in patients with higher lesions—20 of 29 patients with no innervation below the twelfth thoracic roots had died, whereas only 24 of 77 with no innervation below the second sacral nerve roots had died.

When spina bifida affects the upper cervical segment, cerebellar ataxia may be present as well as weakness and spasticity of the legs and arms. The sensory disturbances are confined to the upper cervical dermatomes. Smith[1] has suggested a grading scale of disabilities related to spinal segments of myelomeningocele patients. He divides them into four groups, to highlight four different gradings of severity ranging from total paraplegia to the child who requires no locomotor support at all (Table 1).

Analgesia and loss of awareness to heat may be found over the ankles and feet and, in many cases, this sensory loss extends up over the posterior surface of the legs and thighs to the buttocks and perineum. Tactile sensibility is less affected than pain sense.

Proprioceptive awareness is usually not affected except in cases with severe involvement. The distribution of sensory disturbances is usually of the segmental type.

Usually sphincter control is inadequate unless the symptoms are very mild; complete incontinence of both bladder and bowel occurs if the legs are paralyzed. When the lesion is confined mainly to the conus, loss of sphincter control may be the only evidence of myelodysplasia; the anus is relaxed and the rectum may prolapse.

Hydrocephalus occurred in 77 percent of the cases in Menelaus' series[2] and its incidence was related to the neurological level, there being a 90 percent incidence in higher lesions and 50 percent in the lower ones.

In a group of 134 children who were five years of age or older, reported by Lorber,[4] the average intelligence quotient (IQ) of 59 children who had either no hydrocephalus, or moderate hydrocephalus which required no treatment, was 87 (range 50 to 129); 83 percent of the group had an IQ of

80 or more, and only 5 percent were severely retarded. Included in this study were another 75 children with surgically treated hydrocephalus whose IQ averaged 79 (range: too low to test, to 124); 53 percent had an IQ of 80 or more and 47 percent were retarded, including 17 percent who were grossly retarded.

Selection of Cases for Treatment

A child born with SBC faces a lifetime of being handicapped and being treated. Coping with life is difficult enough for those who are normal; how much more difficult when there is a motor disturbance, a sensory disorder, poor bowel and bladder control, and sometimes mental retardation! The family's coping ability is also severely tested when the child requires periodic surgical therapy, bracing, physical therapy, and special schooling, and may as an adult still continue to be dependent on others.

The survival rate of these children has increased in recent years, because more and more infants are being treated surgically. The medical attitude regarding treatment varies. Zachary[5] recommends that all affected patients be operated upon, even if many of the survivors will suffer from multiple handicaps. Matson[6] considers it wrong to treat infants whose predictable quality of life would be poor.

Lorber,[4] in referring to a personal communication from Ingram, indicates that there are several medical centers which exercise variable degrees of selection. A severe degree of paralysis is the most generally adopted reason for withholding treatment, but incontinence, severe hydrocephalus, gross deformities and poor social conditions are also taken into account. Lorber notes that some would prefer not to treat the most severe cases, but are afraid that surviving normal untreated infants would have greater handicaps than if they had been given total care. He emphasizes that the future quality of life of many of the patients with myelomeningocele depends, at least partly, on the speed, efficiency, and comprehensiveness of treatment from birth and often for the rest of their lives.

Obviously, many will still be severely physically handicapped or mentally retarded, or both, in spite of everything that is done. With the survival of these patients, there is a significant effect on the lives of both patient and family. The community also becomes involved in sharing in the cost of care and providing special programs, such as schools for the handicapped, out-of-home placement, and workshops and agencies which will provide appropriate emotional support through their social and guidance workers.

Lorber[4] made an attempt to determine whether it would be possible to foretell from simple physical signs on the first day of life what the likely future of a baby would be if he were untreated, and to compare this with his chances if he were given total care as it is known today. He analyzed two groups, one consisting of 323 infants treated between 1959 and 1963, and the other, of 201 infants treated during 1967-1968. In all cases, treatment was started on the first day of life, but the treatment for the first group was not considered to be as good as it was for the second group. In the first series, 50 percent survived to two years, compared with 64 percent in the second. The proportion with serious intellectual or physical handicaps did not decrease in the second series. Laurence[7] reported on the survival of untreated SBC in South Wales during a seven-year period from 1956 to 1961; out of 426 children born alive, only 25 percent were still living at two years of age.

Lorber[4] stated that a higher survival rate and a better quality of life would be possible with improved techniques and better application of existing knowledge and facilities. Some patients are so severely handicapped at birth that no method of therapy would prevent major permanent multiple handicaps, a short life, or a severely restricted quality of life. If we wished to spare children and their families prolonged suffering and to give better attention to those who are more likely to benefit from total care, Lorber[4] states that it may be necessary to select suitable cases for intensive treatment and to withold treatment from others. He felt that it was possible to forecast with accuracy, from purely clinical assessment, the minimal degree of future handicap in an individual, even if it is impossible to forecast the maximal degree of disability which he may suffer if he survives. He made clear that therapeutic efforts should be concentrated on those who could truly benefit from treatment, that is, the less severely affected. Lorber concluded his work by quoting Matson:[6]

"In our clinic, it is not customary to operate upon newborn infants or those in the first few months of life with thoraco-lumbar or upper-lumbar myelomeningoceles or myeloschises who exhibit complete sphincter paralysis and total

paraplegia below the upper lumbar segments. This is true whether or not there is significant hydrocephalus at the time. When examination in the first day of life, therefore, confirms total absence of neurologic function below the upper-lumbar levels, custodial care only is recommended. It is recognized that some of these totally paralyzed hydrocephalic patients recommended for custodial care survive for considerable periods of time. For these patients and their families, it is the doctor's and the community's responsibility to provide this care and to minimize suffering; but, at the same time, it is also their responsibility not to prolong such individual, familial, and community suffering unnecessarily, and not to carry out multiple procedures and prolonged, expensive, acute hospitalization in an infant whose chance for acceptable growth and development is negligible."

Ethical Considerations

If the decision is made not to treat, then what? Does the physician withhold parenteral fluids if the child does not suck well? Are antibiotics not to be prescribed if a treatable infection develops? Should palliative procedures be withheld—for example, repairing the skin defect on the back and shunting an enlarging head, even if more extensive therapy is not contemplated? If the child survives the first year, should he be refused other treatment—orthopedic, urologic, or whatever might make life more meaningful and more comfortable?

And what of the parents? If it is decided to do nothing, will they receive the same emotional support from the social workers and other members of the team as the family of the child who is undergoing aggressive therapy?

Who is to pay for the care of the child who is left to "sink or swim" in the family whose financial resources are limited and unlikely to be adequate for the costly nursing care that may be necessary? Will the community accept the financial responsibility to ensure that, if the child survives, life will be kept meaningful to him as an individual regardless of his intellectual limitations and physical handicaps?

There is no simple answer to these questions. My feeling is that these children and their families should be evaluated by a team, including at least a pediatrician, an orthopedist, a urologist, a neurosurgeon, and a social worker. After a careful appraisal of all factors, a tentative prognosis should be made; then one of the team members, acting as coordinator, should interpret the findings and prognosis to the parents while the others should be available for whatever specific help they can provide for the parents. The social worker should be involved in the discussions to be aware of what the parents are told; he can then interpret information, which may be confusing, and can continue to provide emotional support to them. On the basis of the prognosis and the outline of therapy that may be found to be necessary, the physician should assist the family in making a decision as to what treatment is to be carried out. Whatever decision the parents make, it is important that they be relieved of any sense of guilt.

Once the decision is made, the care of the child should proceed in the most humane way possible. Cost of the treatment should not be a limiting factor in the decision. Community support, such as that provided through Crippled Children's Services, should be available to all who need it. Help should not be limited to medical, surgical and hospital care, but should also include counseling and guidance by social workers and public health nurses, out-of-home nursing care whenever indicated, respite and homemaker services, and education and recreational services.

As long as modern ethical practice permits destruction through abortion of unborn children who are likely to be physically and mentally handicapped, and requires that liveborn, obviously defective children not be deliberately destroyed, then every effort should be made to make the life of the individual as meaningful as possible under the specific circumstances. The child should have as much freedom from pain and discomfort as medical and nursing care can provide, and the family should have an opportunity to share their burden of care with dignity and with compassionate assistance from the community.

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Refer to: Heat stroke—Medical Staff Conference, University of California, San Francisco. West J Med 121:305-312, Oct 1974

Medical Staff Conference

Heat Stroke

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Incredible as it may seem on this chilled June day in San Francisco, the topic of our first presentation is heat stroke. Dr. Clinton Lawrence will give the case summary.*

DR. LAWRENCE:† The case for today is that of a 22-year-old white man, a physical education major at the University of California, Berkeley, who was in good health until he collapsed near the finish line of the Bay to Breakers Race. That particular day was sunny but windy. The patient was said to be perspiring profusely at first and was confused. He was covered immediately with down coats and taken to the emergency room at another medical center. He apparently vomited and was incontinent of stool, but there was no seizure activity. His only memory of the event was of a sudden impact. On admission here he denied the use of amphetamines, antihistamines or other drugs. His medical history showed episodic wheezing during the spring for the past four years, but he had not taken medications or seen a physician for this condition. There was also a questionable history of black, tarry stools. The patient reported that upon exposure to extreme cold in Colorado during the skiing season a few years previously, he had had abnormally cold and blanching fingers.

Physical examination on admission here showed blood pressure of 130/70 mm of mercury, pulse rate of 150 per minute, respiratory rate of 32 per minute and temperature of 40°C (105°F) rectally. The patient was well-muscled, tachypneic and appeared confused. The skin was extremely hot and dry. The pupils were dilated but reactive, and there was no evidence of trauma. The neck was supple. On examination of the chest, diffuse inspiratory and expiratory wheezes were heard. Results of cardiac and abdominal examinations were normal. There was 3 plus guaiac-positive stool and nasogastric aspirate. The remainder of the examination showed no abnormalities except for disorientation and symmetrically decreased reflexes.

Admission laboratory data included a hematocrit of 49 percent, and a leukocyte count of 15,000 per cu mm with a normal cell differential. The prothrombin time was slightly prolonged at 12.7 seconds with a control of 11 seconds. At admission, electrolytes showed a sodium level of 147, potassium 5.1, bicarbonate 23 and chloride of 107 mEq per liter. Blood urea nitrogen (BUN) was 27 and creatinine was 2.5 mg per 100 ml. On

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†E. Clinton Lawrence, MD, Intern in Medicine.

urinalysis there was a positive reaction for protein and there was a positive Dipstix® reaction for heme products, but only a few red cells and granular casts were seen in the sediment. The patient was hypoxic and there was respiratory alkalosis. The serum content of muscle enzymes was slightly elevated, as were serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH) and creatine phosphokinase (CPK), but with normal aldolase at that time. An electrocardiogram showed a pronounced right axis and an x-ray film of the chest was clear. The patient was treated at first for heat stroke with intravenous fluids and mannitol to maintain diuresis. He was placed on a cooling blanket in the Intensive Care Unit and iced down with cool towels. There was an immediate response with a decrease in temperature and a clearing of the sensorium. Subsequently the patient did fairly well.

Several problems developed during the patient's stay in hospital. Renal impairment resolved somewhat and there was a BUN of 21 and creatinine content of 1.3 mg per 100 ml on discharge. There were 3.3 grams of proteinuria per 24 hours and normal creatinine clearance. Rhabdomyolysis developed, manifested by very tender and swollen thighs with extremely elevated serum content of muscle enzymes. The urine at first was clear but became quite dark again with a positive hemestick reaction, but no red cells were noted. A myoglobin determination is pending. Also, liver dysfunction developed, with jaundice. The liver was of normal size but tender, and the bilirubin content was 5.5 mg per 100 ml of blood, mainly direct. There was well developed evidence of disseminated intravascular coagulation but with no bleeding. Prothrombin time, partial thromboplastin time and thrombin time were elevated, with low platelet count and low fibrinogen and elevated fibrin-split products. All of these problems resolved during the patient's stay in hospital, and most of the serum enzyme levels were returning toward their normal ranges at the time of discharge. The only other problem was the wheezing noted on admission with the right axis deviation shown in an electrocardiogram. A lung scan was negative for pulmonary emboli. Creatine phosphokinase fractionation showed the source was predominately skeletal muscle, but there was a small cardiac fraction.

We have the patient with us today for those of you who might like to ask him a few questions.

DR. SMITH: *This patient will be discussed by Dr. Floyd C. Rector, Jr. Dr. Rector is Professor of Medicine and Chief of the Renal Division at Moffitt Hospital in our Department of Medicine. Dr. Rector joined us from Dallas last August. He assures me that this problem is not so rare in Texas as it is in San Francisco. Dr. Rector, would you like to ask any questions of the patient?*

DR. RECTOR:* How long had you trained for the race?
Patient: About three months, seriously.

DR. RECTOR: How frequently would you run in your training?
Patient: Five days a week.

DR. RECTOR: Had you taken any salt tablets at any time during your training period?
Patient: No.

DR. RECTOR: Was there anything different during the race as compared to your training period?
Patient: The only difference would be that we ran through Golden Gate Park twice and the finish line was about 400 yards past where we had trained to finish; so when we got to the point where we thought the race would finish, there were about 400 yards remaining.

DR. RECTOR: Did you sprint this 400 yards?
Patient: Yes, I tried.

DR. RECTOR: Do you remember anything in the period of time after you collapsed and before you arrived at the hospital here?
Patient: I do remember after I had gone down several people trying to get me out of the way of all the other runners. I thought I was conscious at the emergency hospital and they said I was not, so I guess you call that hallucinations. I guess I was doing a little of that.

DR. RECTOR: How have you done since you left the hospital here?
Patient: I have tried to run about three or four times.

DR. RECTOR: Have you?
Patient: Yes, and it has been a mild jog.

DR. RECTOR: Do you have any muscle problems now?

*Floyd C. Rector, Jr., MD, Professor of Medicine, Chief of Renal Division, Department of Medicine.

TABLE 1.—*Three Syndromes Associated with Heat*

Heat Cramps

Muscle cramps following exertion in hot weather due to salt depletion

Heat Exhaustion

1. Water depletion—Thirst, fatigue, weakness, anxiety, hyperventilation, paresthesias, agitation, psychosis, *hyperthermia*
2. Salt depletion—Muscle cramps, weakness, headaches, giddiness, anorexia, nausea, vomiting and diarrhea, hypotension, tachycardia, *body temperature normal*

Heat Stroke

Hyperpyrexia (rectal temperature greater than 41.1°C), anhidrosis (present in only 50 percent of cases), delirium, coma

Patient: Just a little tenderness. I have lost a lot of weight in my legs.

DR. RECTOR: Do you still have any discrete tender spots?

Patient: No, not really.

DR. RECTOR: Are there any signs of nodules developing in your legs?

Patient: No.

DR. RECTOR: Thank you, Mr. E.

DR. RECTOR: Mr. E. had a rather serious heat illness which was precipitated by exceptional exertion. The degree of exertion appears to be greater than he had experienced in his training period. This illness was characterized by delirium, hallucinations, diminished consciousness and finally a stuporous state, hyperpyrexia and extentensive tissue damage. He had evidence of diffuse capillary endothelial damage with secondary intravascular coagulative syndrome. He had evidence of a mild myocardial involvement, as well as some elevation of liver enzymes. There was extensive rhabdomyolysis with myoglobulinuria and a transient episode of renal insufficiency which rapidly cleared. This syndrome was called heat stroke, although it is not typical of the classic definition of heat stroke as originally defined by the British Medical Council.

Table 1 lists three syndromes associated with heat.[1] There are heat cramps, heat exhaustion and heat stroke. Heat cramps follow fairly strenuous exertion in hot weather, occur primarily in well-acclimatized, physically fit individuals, are associated with muscle cramps, are due entirely to salt depletion and can be corrected by salt replenishment. The second syndrome is heat exhaustion, of which there are two forms. One form, which is due mainly to water depletion, tends to occur in older debilitated people or young children who, for one reason or another, are unable to replenish sweat losses by drinking. They become dehydrated and hypernatremic, have intense thirst, fatigue and weakness, become irritable and develop parethesias, agitation, hyperthermia and sometimes psychosis. The second form of heat exhaustion is related to salt depletion, which in some individuals reaches deficits as great as 1,000 mEq. The symptoms, which can be attributed largely to extreme contraction of extracellular volume, include muscle cramps, weakness, headaches and orthostatic hypotension. The body temperature tends to be normal or even subnormal. Either of these two forms of heat exhaustion may progress to heat stroke, which classically is defined as hyperpyrexia with a rectal temperature greater than 41.1°C (106°F), cessation of sweating, delirium and coma.

The illness of Mr. E. was called heat stroke, although the recorded temperature was only 40 to 40.5°C, or about 105°F. He continued to sweat immediately after the first episode of collapse but had ceased to sweat by the time he arrived at the emergency room, and he did have the typical central nervous system symptoms. The classic definition of heat stroke refers primarily to the type of heat stroke that develops in older individuals, alcoholics and people with chronic debilitating illnesses, particularly those with underlying heart disease. In these people, heat stroke tends to develop during extended periods of high environmental temperatures in which both the day and night are hot. They sweat over a period of three or four days, gradually there is exhaustion of sweating and heat stroke develops. These patients classically have anhidrosis and dry skin when first seen.

In recent years, however, another type of heat stroke associated with extreme exertion has been seen with increasing frequency. This usually occurs in young athletes, particularly football players during spring training and in the beginning of the fall football season, and young recruits in the military who undergo basic training in the Southern states during the summer months. When heat stroke develops in these persons, the rectal temperatures may not be as great as 41.1°C, yet there still is considerable tissue damage from hyperpyrexia. First, it seems that in severely exercising persons there is a pronounced

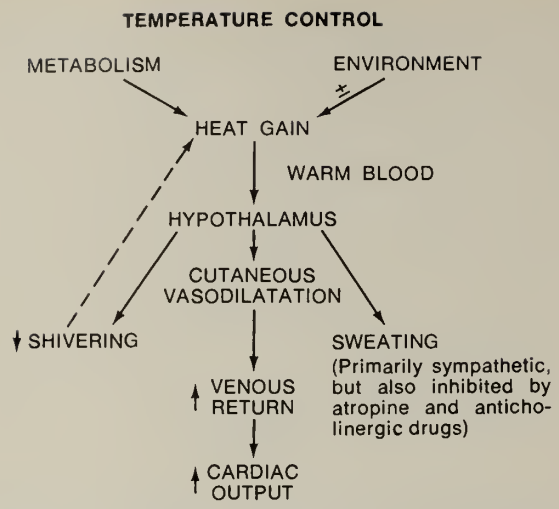

Figure 1.—Diagrammatic representation of temperature control in man.

temperature gradient between hepatic and rectal temperatures. In young men vigorously exercising in a hot climate Rowell et al[2] found that the temperature of the hepatic venous blood may be 106 to 107°F, while rectal temperature is only 102 to 103°. Second, when heat stroke develops in young persons after severe exertion, there is not necessarily sweat exhaustion and they may be sweating at the time the heat stroke develops. Thus, there are some differences between the classic form that occurs in older debilitated individuals or alcoholics, and the form occurring in young athletes.

As a background to considering the pathogenesis of heat stroke, it is helpful to consider a few aspects of temperature control (Figure 1). The body gains heat either from that produced by metabolism or from the environment if the environmental temperature is greater than body temperature. The blood which is warmed by this process is monitored in the anterior hypothalamus where there exists a temperature-sensitive area responsible for coordinating heat dissipation. When warm blood enters the hypothalamus, the latter will stimulate sweating. The sweating is primarily sympathetically enervated so that any sympatholytic drug may block it, but it is also inhibited by atropine and anti-cholinergic drugs. The essential purpose of sweating is to cool the skin. The second phase of heat dissipation is to increase the flow of blood to skin where it can be cooled. Thus, cutaneous vasodilation increases venous return and cardiac output so that there is a high output state. Finally there is decreased shivering which reduces heat production. These are the three components integrated at the hypothalamic level that serve to regulate body temperature.

TABLE 2.—*Causes of Heat Stroke*

I.	Increased heat production
	A. Extreme exertion
	B. Agitation—delirium tremens, psychosis, drugs (LSD, amphetamines)
II.	Impaired heat dissipation
	A. Impaired sweating
	1. Skin diseases, cystic fibrosis
	2. Drugs—atropine, belladonna
	3. Mechanical—surgical drapes, football uniforms
	B. Cardiovascular disease
	C. Central nervous system—cerebrovascular disease, alcohol, tranquilizers

Heat stroke may occur as the result of abnormality at one site or several different sites. There might be production of energy at a rate greater than it can be dissipated or there might be some interference with the dissipation process.

Table 2 shows some of the causes of heat stroke. Heat stroke may result from increased heat production, either from extreme exertion, as illustrated by our patient today, or from extreme agitation. This is sometimes seen in patients with alcoholic withdrawal and delirium tremens. If hyperpyrexia develops during the course of delirium tremens, it is associated with a very high mortality rate. There are certain psychotic patients who have become agitated and developed heat stroke, and finally certain drugs, particularly LSD (lysergic acid diethylamide) and amphetamines, have induced sufficient agitation and hyperactivity to precipitate heat stroke. Heat stroke also may develop from impaired heat dissipation. This can be due to impaired sweating. A variety of skin diseases involve the sweat glands and prevent sweating, or there may be congenital absence of sweat glands. Cystic fibrosis does not necessarily impair sweating but because of very high sweat, sodium chloride concentration may lead to salt depletion. Effective sweating may be prevented by either certain drugs or mechanical covering of the skin. At one time when surgical suites were not air conditioned, a number of patients developed heat stroke as a consequence of impaired heat dissipation secondary to the surgical drapes. Football players may also have impaired sweating as a result of their uniforms. Approximately 30 percent of the sweating skin is covered by nonporous

TABLE 3.—*Exertion-Induced Heat Stroke*

I. Electrolyte and acid-base disturbances
   A. Hyperventilation, with respiratory alkalosis
   B. Lactic acidosis
   C. Hypo- or hyperkalemia
   D. Hypocalcemia early; hypercalcemia later
   E. Hyperuricemia
   F. Elevation of muscle, hepatic and cardiac enzymes

II. Hematologic
   A. Leukocytosis; eosinophilia
   B. Diffuse capillary endothelial damage with hemolysis, thrombocytopenia, consumptive coagulopathy, fibrin-split products

III. Central nervous system
   A. Delirium, stupor or coma
   B. Convulsions—localized or generalized
   C. Cerebellar dysarthria and ataxia—may be chronic

IV. Cardiac
   A. Subendocardial necrosis
   B. High output failure with hypotension and tachycardia

V. Hepatic—mild to fulminant necrosis

VI. Muscle—rhabdomyolysis; calcification

VII. Kidneys—
   A. Acute renal failure—rare in non-exertional heat stroke
      1. Myoglobinuria
      2. Uric acid nephropathy
      3. Diffuse intravascular coagulation
   B. Chronic progressive interstitial nephropathy—10 percent

leather in the usual football uniform, and this may seriously impair heat dissipation. Patients with cardiovascular disease may be unable to deliver the necessary quantity of blood to the skin surface for cooling. Finally, there may be disruption of the central nervous system or the hypothalamic integration center by cerebrovascular disease, alcohol or tranquilizers. Therefore, any of the above circumstances may lead to heat stroke.

Table 3 shows some of the features that we now associate with exertion-induced heat stroke. There are a variety of electrolyte and acid base disturbances. Such patients uniformly hyperventilate and have a respiratory alkalosis. This may have very serious consequences as far as its effect on cerebral blood flow and may contribute to the altered sensorium. Lactic acidosis may develop in some patients. It is of interest that in the case of our patient today there was only respiratory alkalosis without lactic acidosis. This may have been due to the two- or three-hour delay in arriving at our emergency room. The patients may have either hypokalemia or hyperkalemia. Approximately half of the cases of young recruits or athletes that develop heat stroke have evidence of potassium depletion, and this may play an important role in the development of their hyperpyrexic state. Against this background if extensive rhabdomyolysis develops, if there is extensive hemolysis or if lactic acidosis develops with a shift of potassium out of cells, hyperkalemia may supervene, even against the background of serious potassium depletion.

One thing that has not been widely recognized is that hypocalcemia with tetany may occur early in the course of heat stroke, particularly in those persons in which the heat stroke is induced by exertion. This is primarily due to deposition of calcium in damaged muscles. There are studies showing that labeled calcium will migrate and precipitate in damaged muscle in this condition. Later hypercalcemia may develop in such patients. It is probable, although unproven, that the initial hypocalcemia induces hyperparathyroidism which then does not shut off immediately and results in a transient period of secondary hyperparathyroidism, causing rebound hypercalcemia. With Mr. E., there did not appear to be initial hypocalcemia; in fact, transient hypercalcemia was indicated. Initial calcium was about 11 mg per 100 ml. This was probably a reflection of the concentration of plasma proteins.

In patients with exertion-induced heat stroke, there may be very high rates of uric acid production and serum uric acid levels. In our patient, there was a serum uric acid of 12 mg per 100 ml. This is very common and may contribute to uric acid nephropathy. Then, of course, there are elevations of the serum enzymes, originating from muscle, liver and heart. There are considerable hematological changes. There is almost always leukocytosis with a left shift and eosinophilia. There is also evidence of diffuse capillary endothelial damage, as shown by electron microscopy. Secondary to this there may develop diffuse intravascular coagulopathy.[3] This was present in the case discussed today. It may lead to widespread bleeding diathesis. In fact, in some of the earliest cases of heat stroke reported in the 1700's, bleeding was a very prominent symptom.

There also are pronounced central nervous system disturbances, including delirium, stupor, coma, convulsions—either localized or generalized—and cerebellar symptoms (dysarthria and ataxia). In particular, the cerebellar symptoms may persist and be chronic. The heart frequently

shows evidence of subendocardial necrosis and hemorrhage, and in a few instances involving young men, there have been through-and-through myocardial infarctions without evidence of underlying coronary artery disease. At the time of heat stroke there is a high output state with a high cardiac output, low blood pressure and a tachycardia. Hypotension may be very serious in some instances. There may be mild to fulminating hepatic necrosis. Some individuals have actually died in hepatic coma. There is extensive rhabdomyolysis. Early, calcium may precipitate in the damaged muscle and later there may be evidence of muscle calcification.

Acute renal failure is very common in the exertion-induced heat stroke, but it is rare in the classic form that occurs in older persons or alcoholics.[4] It appears that the renal failure that develops is not a result of the hyperpyrexia per se, but is related more to associated muscle damage, myoglobulinuria,[5] increased uric acid production with superimposition of uric acid nephropathy and diffuse intravascular coagulation. Renal function appears usually to recover almost totally. However, there is a report from South Africa in which 40 patients from the diamond mines had heat stroke with renal failure of an exertional type; in 10 percent of those patients a chronic progressive interstitial nephritis developed, and those were the patients tending to have slightly more severe forms of acute tubular necrosis and higher serum urate concentrations.[1]

The findings listed here characterize heat stroke as it manifests itself not so much in the classic form of a debilitated person, but in a young athlete who exercises strenuously in a hot environment. In evaluating some of the factors involved in causing heat stroke in these persons, it is helpful to review briefly the physiology of heat production, dissipation and acclimatization. If an individual exercises mildly, he may produce heat at a rate of 300 kilocalories per hour, and at peak levels—for example in a 100-yard dash—it may reach 900 to 1,000 kilocalories per hour. If a person were exercising at a mild rate (300 kilocalories per hour), and were insulated so that he was neither gaining nor losing heat from the environment then the temperature would increase approximately 9°F in a single hour. If he were exercising at a maximal rate (approximately 600 kilocalories), then there would be about an 18° rise per hour. In order to prevent these extreme increases in temperature a tremendous amount of heat must be dissipated by sweating and delivery of blood to skin. Sweat rates can reach about 1.5 liters an hour in an unacclimatized person and 2.5 to 3 liters an hour in an acclimatized individual. When vaporized, 1.5 liter of sweat is capable of dissipating maximally about 675 kilocalories per hour. Thus, an unacclimatized individual could dissipate a fairly heavy heat load provided something did not interfere with sweating or evaporation. However, sweat rates tend to drop off rapidly in the unacclimatized individuals because they may become salt and volume depleted. When this occurs, body temperature starts to rise. It is important, therefore, in persons who are going to be undergoing heavy exercise in high temperatures that acclimatization has occurred.

TABLE 4.—*Physical Conditioning and Heat Acclimatization*

I.	Metabolic—increased efficiency
	A. Increased muscle glycogen
	B. Increased muscle mitochondria
II.	Hemodynamic
	A. Increased plasma and extracellular volumes
	B. Increased maximal cardiac output
	Increased stroke volume
	Decreased peak heart rate
III.	Sweating
	Decreased sweat sodium secondary to increased aldosterone

Table 4 shows some of the processes involved in physical conditioning and heat acclimatization. First, there is an increase in metabolic efficiency so that there is better energy utilization. In a trained person there is an increase in muscle glycogen which provides a source of energy for protracted muscle work. There is an increase in muscle mitochondria which serves to switch metabolism from the anaerobic to the oxidative phase, a more efficient process. These changes begin early in the course of physical conditioning but may take as long as two months to become complete. The second aspect of acclimatization is hemodynamic, thus augmenting the ability to increase blood flow both to muscles where heat is generated and to skin where it is dissipated. Two aspects of the hemodynamic adaptation are (1) increased plasma and extracellular volume to compensate for the vasodilatation that occurs when one exercises in a hot climate, and (2) increased myocardial efficiency presumably secondary to increased cardiac mitochondria, thereby resulting in increased maximal cardiac output, in-

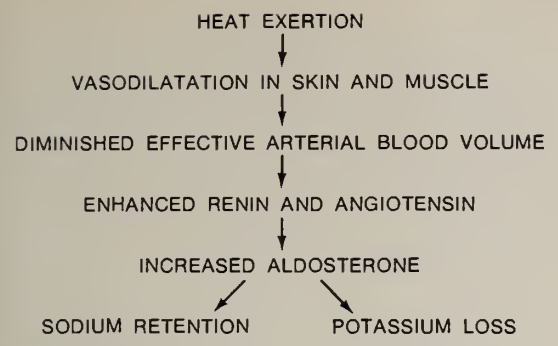

Figure 2.—Mechanisms leading to potassium depletion.

creased stroke volume and decreased peak heart rate during exercise. Finally, the sweating process becomes more efficient, both as far as the rate of sweating and the ability of the sweat glands to conserve sodium. This latter process is totally dependent on aldosterone. Part of this adaptive process, both as far as the increase in extracellular fluid volume and the decreased sweat sodium, depends on an adaptive increase in aldosterone.

The salutary role of aldosterone in promoting heat acclimatization has been known for a long time, but what has not been widely recognized is that the adaptive increase in aldosterone may have certain deleterious effects. This is illustrated in Figure 2. If one exercises in a hot environment there is marked vasodilation in skin and muscle which transiently decreases the effective arterial blood volume, stimulates renin and angiotensin, and an increase in aldosterone. This increase in renin, angiotensin and aldosterone occurs whether the subjects are on a low, normal or high salt diet. The aldosterone will contribute toward salt retention and expansion of the plasma volume, as well as more efficient sweating. The effect of aldosterone, however, persists after the period of exercise, and since these persons tend to be taking in salt, and in many instances very high amounts of salt, this combination of high salt intake with increased aldosterone results in some potassium loss.

In studying two groups of recruits that underwent basic training in San Antonio—one group in winter months and another group in the summer months—Knochel[6] showed that the recruits who had their physical training during the summer months lost almost 600 milliequivalents of their exchangeable body potassium. This occurred within the first week or so, and then by the fourth week the deficit had been spontaneously corrected. The mechanism for the correction is not clear.

TABLE 5.—*Consequences of Potassium Depletion*

I. Kaliopenic nephropathy with impaired urine concentration

II. Decreased response to catecholamines; postural hypotension

III. Metabolic
Decreased glycogen synthesis
Impaired insulin release with hyperglycemia

IV. Decreased aldosterone production with an increase in sweat sodium

V. Myocardial insufficiency

VI. Muscle
A. Increased membrane permeability with leak of muscle enzymes and decreased membrane potential
B. Impaired exercise hyperemia causing rhabdomyolysis and hyperpyrexia

The aldosterone levels increase at first and then drop off some, but there is still enough aldosterone to maintain low sweat sodium. However, for some reason the potassium deficit is replenished despite this state of mild functional hyperaldosteronemia.

Some of the consequences of this degree of potassium depletion are shown in Table 5. Kaliopenic nephropathy may develop, with impaired urine concentration and impaired water conservation. During World War II there were reports of recruits who had very high salt intakes in whom pronounced polyuria developed, with urine volumes up to 8 to 10 liters. Presumably this was a combination of kaliopenic nephropathy and high salt intakes. Potassium deficiency may also impair the response to catecholamines. As a result, there may be postural hypotension. In addition, potassium deficiency has certain metabolic consequences such as diminished glycogen synthesis, impaired insulin release with the hyperglycemic stimulus and carbohydrate intolerance. Potassium depletion may also decrease aldosterone production, which would then secondarily impair the adaptive response to the sweat glands. Knochel has recently shown that myocardial insufficiency with pulmonary edema during severe exertion may develop in dogs with potassium deficiency. Finally, there is pronounced alteration of muscle function with increased permeability of the membrane to enzymes so that there is a leakage of aldolase, CPK and other muscle enzymes in the nonexercising, potassium deficient animal. In addition, hypokalemia impairs exercise hyperemia in muscle and may lead to rhabdomyolysis and hyperpyrexia.

In Knochel's experiments, which were performed in both normal and potassium deficient dogs, the gracilis muscle was stimulated electrically, potassium release was measured in the venous effluent and blood flow to the gracilis was measured in response to stimulation.[7] Stimulation caused a pronounced increase in the release of potassium into the venous effluent in normal but not in potassium deficient dogs. In association with these changes there was a marked increase in muscle blood flow in the normal animals but not in the potassium deficient animals. This failure to increase blood flow could be corrected or partially reversed by infusion of potassium chloride into the muscle.

To summarize, persons training in a hot environment develop moderate potassium deficiency early in the course of their acclimatization. This may impair muscle release of potassium during muscle contraction, as well as cause a slight decrease in myocardial efficiency, so that together these two factors might lead to a decrease in the extent of exercise hyperemia causing muscle ischemia. As a consequence there might be rhabdomyolysis. In addition, the heat that is generated in the core of the muscle would not be effectively dissipated, leading to damage and hyperpyrexia.

Exertion-induced heat stroke is becoming an increasingly serious problem in young athletes. Unfortunately, it has a very high mortality. In certain series as many as 80 percent of the subjects who develop full blown heat stroke have died. This could be prevented by a proper period of acclimatization. There is no evidence that salt loading beyond a certain level facilitates the acclimatization. It is necessary to have a certain amount of salt supplementation, but doubling the quantity of salt into the diet is perfectly adequate. Young athletes, particularly on high school football teams, frequently are deprived of water with the misconception that this will accelerate the acclimatization process. However, *this practice is very hazardous*. It is important that young athletes go through a proper acclimatization period, that they have salt replacement, that they have adequate water intake and that they gradually work up to their full exertional activities. When heat stroke does develop, it is important that cooling be initiated as rapidly as possible by ice packs and evaporative procedures of one type or another. It is important that an airway and an intravenous needle be in place before the patients are placed in an ice bath; the procedures may be difficult to do later when they begin to convulse or vomit. There is no convincing evidence that hypothermic drugs or steroids have a beneficial effect.

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Important Advances in Clinical Medicine

Epitomes of Progress— General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in General and Family Practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in General and Family Practice which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Newer Techniques of Treatment of Sexual Dysfunction

TODAY'S RAPIDLY CHANGING SEXUAL MORES may often bring patients to their family physician with questions about their sexuality.

Sex counseling clinics based on the concepts of Masters and Johnson are able to handle only a few hundred couples each year. Few physicians have been exposed to any formal courses in sex education. As such, sexual maladjustment may be a frequent cause of anxiety and depression and the physician should not be uncomfortable in discussing any form of sexual expression. To be an effective therapist requires being at ease and having some knowledge of the problem. The physician should not depend on his own experience and "hang-ups." Because there are not enough sex counselors, the family physician will be called upon increasingly for help. Some familiarity with counseling techniques, starting with the interview of both partners, is essential. To prepare for the role, courses offered by medical schools on the restructuring of sexual attitudes can be very helpful.

There is a wide range of therapy for such problems of sexual dysfunction as impotence, premature ejaculation or orgasmic failure aside from the traditional approach of long-term psychotherapy. A new approach is "pair therapy" following the methods of Masters and Johnson.

RAYMOND C. ANDERSON, MD

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"Rule Out" May Be a "Cop Out"

TWO TRENDS in medicine and especially in the field of family practice have converged in such a way as to challenge the validity of a time-honored diagnostic stance, namely: "rule out." These two trends are the widespread adoption of the problem-oriented record and the general recognition that a major portion of physician-patient encounters do not fit the traditional medical model.

Following the traditional model, one "ruled out" all reasonable and some not so reasonable organic diagnoses by a series of diagnostic, historical, physical diagnostic and laboratory procedures; a plan which was often quite time consuming, frustrating and expensive. Once this diagnostic game was exhausted one then announced to the patient that the problem must be entirely emotional since there were no valid diagnoses uncovered by the diagnostic exercise. Needless to say this announcement was not always readily accepted by the patient and all too frequently this same diagnostic guessing game was renewed with another set of physicians.

The problem-oriented system demands that we look at the total situation in a holistic manner from the very onset. Thus psychological factors, such as anxiety and depression; behavioral factors, such as problems of living manifest as symptoms; and psychosocial factors, such as loss, deprivation and loneliness, are recognized in their own right and by their own valid diagnostic criteria without waiting for the exhausting process of "rule out."

This approach in no way diminishes the importance and significance of an accurate history. To the contrary it enhances the value of the history by giving it a broader base.

This approach in no way maligns the value of an accurate physical examination and the usefulness of appropriate laboratory tests.

This approach simply reassembles the priorities and insures that regardless of what physical, chemical or structural deviations are discovered, they are all viewed in the context of the patient's lifestyle, his family relationships, his position and responsibilities in society and the stresses and emotions which go with his societal role.

J. BLAIR PACE, MD

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Xeromammography, an Improved Method of Detecting Breast Cancer

EARLY DIAGNOSIS of breast carcinoma seems to offer the best chance of survival. Xeroradiography, an improved radiologic technique, has proven helpful in the diagnosis of breast lesions, particularly carcinoma. Some carcinomas, which were not diagnosed from conventional mammograms, were more clearly evident on xeromammograms. Carcinomas in dense fibrous breasts have been more readily identifiable. Easy readability has added to the benefit of this method. A recent study of 250 patients revealed 13 clinically occult carcinomas. Self-examination by the patient and examination by the physician who has a high index of suspicion is essential for early diagnosis. Xeromammography appears to be a superior method (compared to mammography) for the diagnosis of carcinoma of the breast. It offers the practicing physician another aid in breast cancer diagnosis.

BENSON MCGANN, MD

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Soap Photodermatitis

THE INGENIOUS CHEMISTS of industry have created a large variety of chemical products which have a characteristic of reacting with the outer layers of skin to induce a long acting antibacterial effect that does not readily rinse away. The value of such an antibacterial was well demonstrated in the recent, controversial withdrawal of hexachlorophene from use in nurseries. A far more widespread use of these materials is in the highly advertised deodorant and antiseptic soaps.

There are two general types. One is the bisphenol, of which by far the best known and most widely used is hexachlorophene. The value of this product is well established. Hexachlorophene has a fairly good record as far as photosensitivity is concerned although this author has seen heavy pigmentation and thickening of the skin in a nurse who used it routinely for face care over a period of years.

The second major group, the brominated salicylanilides, are much more active as photosensitizers. There is a fairly long list of cosmetics which use brominated salicylanilides. The list includes

detergents such as Bon Ami®, Cold Power® detergent and Lux® detergent as well as popular face soaps, such as Lux® soap, Shield® soap and Zest.® Zest® is very heavily advertised on television and in this author's experience is a common offender.

The butterfly rash over the cheeks and bridge of the nose may suggest at first glance that we are dealing with lupus erythematosis. As one would expect, the areas affected are those most directly exposed to the sun's rays, including the tips of the ears, the cheeks and backs of the hands. Unfortunately photosensitivity may persist for a considerable length of time after the use of the offending soap or detergent is discontinued. A few unfortunate victims become identified as persistent light reactors and must avoid exposure for months or years.

J. Blair Pace, MD

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Evaluation and Management of Insomnia

Insomnia is the most prevalent of all primary sleep disturbances which the physician is called upon to manage. Recent studies in sleep research laboratories have contributed greatly to our understanding of this disorder. It has been found that over 80 percent of insomniac patients have significant psychopathology as evidenced by one or more major Minnesota Multiphasic Personality Inventory (MMPI) scales in the pathological range. Specific MMPI scales which have been found most frequently abnormal are those for depression, sociopathy, obsessive-compulsive features and schizophrenic trends. Insomniac patients, however, seldom view their difficulties in psychological terms. They are not often referred for psychiatric care and seek such care only rarely.

Although many drugs are initially effective in inducing or maintaining sleep, tolerance frequently develops within two weeks. Flurazepam (Dalmane®) seems to be the drug of choice since such tolerance does not appear to develop. In cases where hypnotic drugs have become ineffective, the drug should be withdrawn extremely gradually (at the rate of one therapeutic dose every five or six days) to minimize rapid eye movement (REM) rebound, and the patient should be warned that increased dreaming and even nightmares may occur. Drug therapy alone is usually sufficient in cases of mild insomnia or insomnia secondary to situational disturbances. More severe or chronic insomnia usually requires both psychotherapy and drug therapy.

John Geyman, MD

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Spandex Dermatitis

Some knowledge quite old becomes extremely current due to progress in industry. A good illustration of this is provided by the special organic sulphur compounds which include disulfiram (Antabuse®), thiram, and now spandex used in making stretch materials for garments—especially girdles and brassieres for women. It is well known that the patient ingesting disulfiram (Antabuse®) is sensitized and becomes extremely ill when he ingests alcohol. It is less well known that related synthetic rubber compounds, or related fungicides, such as thiram, have this same ethanol sensitization reaction in the skin.

As early as 1925 workers in the rubber industry began to develop eczematous eruptions due to sensitivity to thiram (bis [dimethylthiocarbamoyl] disulfide). This material is a catalytic accelerator for the process of vulcanizing and it is still in use and constitutes a major cause of rubber sensitivity.

In the 1950's this molecule produced the interesting condition known as "golf course dermatitis." Thiram is an excellent fungicide and was sprayed on golf courses for this purpose. The golfer who played early in the morning seemed to get the largest dose and if the golfer had an alcoholic drink after the game the burning, itching and redness of the skin that soon ensued was very distressing. An interesting aspect of this was that the hand that was used to pick up the golf ball was always much more involved than the other hand.

Now modern industry has given us spandex manufactured by several different companies including Dupont, United States Rubber, American Cyanamide and Kemstran Corporation and sold under various trademarks including Lycra,® Burreme,® Numa® and Blue "C"®. By 1967 it was

thought that products of other manufacturers who produced spandex containing mercaptobenzothiazole were responsible for the allergic reaction to spandex garments. Since 1967 it has become very evident that this is not the case and even though the products listed above contain none of the offending mercaptobenzothiazole one still sees the burning, itching, eczematous rash tracing the specific outline of the spandex bra. These reactions are especially severe if the new spandex bra or girdle is worn on an evening when the patient had alcoholic drinks.

This old nucleus, the polyurethane nucleus, is still very much with us and when one sees dermatitis on the area covered by a brassiere or girdle one is well advised to read the label and look for the word "spandex."

J. Blair Pace, MD

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Health Hazard Appraisal—Prospective Medicine

A new aid in patient care that evaluates the risk of an illness before it strikes has been developed and is called "health hazard appraisal." This method is one of the newer developments in medicine's continuing attempt to carry preventive medicine into the prospective field.

In several areas of the country, methods have been developed for using a computer to evaluate a patient's risk of disease. The data obtained can be discussed with the patient so that he may determine the desirability of changing his life style to decrease the risk of the more common causes of death.

The patient's personal physician takes the information (which includes physical findings, laboratory findings and a health questionnaire that surveys family history and personal habits) and this is entered into a computer. The individual's risk factors are determined and outlined in such a manner that the patient may determine his life expectancy with his current risk. The patient is also given an estimate of the additional life expectancy he would have if he corrected the correctable factors.

This computerized technique is now available to any physician who desires it through laboratories throughout the country.

Prospective medicine is merely another way in which the modern physician may be able to increase the longevity of his patients and attempt to truly prevent illness.

Simon Brumbaugh, Jr, MD

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Cromolyn in the Prevention and Treatment of Asthma

Cromolyn sodium (Intal®, Aarane®) is a recently approved antiasthmatic drug which has now been released for general prescription use in the United States. This drug has a mechanism of action unlike any previously used mode of antiasthmatic therapy. Cromolyn sodium (cs) has been in general use in Europe for several years and in Great Britain since 1968. It appears useful in the prevention of asthmatic attacks, especially pollen allergy asthma which comes on a seasonal basis. Cromolyn is administered as a dry powder, combining twenty milligrams of cromolyn sodium and twenty milligrams of lactose in a capsule. A special inhalation device permits inhalation of the powder in about five or six deep breaths. Administration is one capsule four times a day at regular intervals. The drug cromolyn is not of great use in the treatment of established asthmatic attacks and has no bronchodilator effect. Its mode of action is generally conceded to be by stabilizing the membrane of the mast cells in the bronchial wall. This blocks the antigen-antibody release of histamine by preventing disruption of these mast cells.

Effectiveness of cs can be demonstrated by pretreatment with inhalations of powder and then challenge, using pollens known to produce asthma in a given patient. The most startling effectiveness of the drug has been in young asthmatics with relatively little element of infection and with severe restriction of exercise tolerance. cs seems to prevent the usual delayed asthma attack from prolonged exercise and many of the treated children are released for full participation in games and running by the administration of the protective medication.

The second and very promising use of cromolyn

is in the reduction or elimination of the need for corticosteroids. CS has no steroid effects and in the years since 1965, when clinical trials began, it has shown a minimum of undesirable side-effects.

In certain instances it has released life-long asthmatics in their mid-twenties from being severely restricted in all activities, caused a complete absence of asthma symptoms and allowed numerous physical activities which were heretofore impossible. CS may offer great hope for the young asthmatic whose lungs have not sustained the damage of years of repeated asthmatic attacks. There is the possibility of delaying or even preventing lung damage as the patient becomes older and continues therapy.

Principal noted side-effects of CS have been an occasional complaint of rawness and irritability of the pharynx and trachea in a few patients. An occasional patient is intolerant to the inhalation of the dust, either when a placebo of plain lactose is used or when the effective agent combining lactose and cromolyn is used.

The cost of the material is sufficient to discourage random or inappropriate use. The poorest results from the use of this agent would appear to be in patients with chronicity and with a large element of infection involved. It, in other words, does not appear to be an effective treatment for asthmatic bronchitis.

CHARLES CRONIN, MD

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Intravenous Regional Anesthesia

ALTHOUGH INTRAVENOUS REGIONAL ANESTHESIA has been in limited use for a number of years, it has recently received increasing recognition as a safe, effective and simple procedure. A regional block of an extremity distal to a tourniquet is produced following the intravenous injection of a local anesthetic into an exsanguinated limb.

This technique is seeing more common use by family physicians, emergency care physicians, surgeons and orthopedists. It is particularly useful in surgical operation or manipulations of the upper or lower extremities. It may be indicated for procedures involving the extremities lasting less than one and three-quarters hours, when general anesthesia is contraindicated (such as by recent ingestion of a meal) or when an anesthesiologist is unavailable for emergency procedures. This procedure has several advantages over other anesthetic approaches: it is easier to do than other regional nerve blocks, it is rapid in onset and generally effective, lower anesthetic blood levels are achieved using it than with lumbar epidural or axillary blocks, the recovery time is short and complications are both infrequent and readily managed if meticulous attention is given to proper technique.

JOHN GEYMAN, MD

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Enteropathogenic Escherichia Coli (EPEC) in Infants' and Travelers' Diarrhea

E. COLI are normal inhabitants of the bowel. More than twenty different enteropathogenic serotypes are now classifiable at many local laboratories. Several are incriminated in lethal diarrhea in infants and enteropathogenic strains often cause travelers' diarrhea, more commonly known as "turista." Evidence continues to mount associating EPEC with most cases of "turista" but no large scale study has yet been conclusive. Eighty percent of all acute diarrhea in some hospitals is so-called "non-specific" diarrhea. Therefore, some investigators believe that E. coli is actually responsible for most acute diarrheal diseases.

EPEC has two different reactions on the gut. It can produce an enterotoxin, which is actually an exotoxin with a cholera-like virulence and activity on the small bowel. This causes enterosorption (a passage of fluid and electrolytes into the lumen of the intestine). EPEC also may react by direct invasion of the cells of the mucosa and produce a Shigella-like diarrhea, affecting the colon.

The toxins of E. coli are at least as potent as cholera toxins but much less antigenic. Unlike cholera, EPEC causes poor antibody response, and this may explain the frequent recurrences in the same patient. Multiple type-specific bacterial vaccines, against all the enteropathogenic serotypes, would be impractical, especially when the possibility of the emergence or discovery of new enteropathogenic serotypes is considered. The best

prophylaxis against "turista" is to eat only what is peeled or cooked, and to drink only boiled water, beverages that have been boiled, beer or wine. Tap water, used in brushing the teeth and for ice in drinks, can be a source of infection. The prophylactic use of antimicrobial drugs to prevent diarrhea is of questionable value.

On culture, if the finding is pure E. coli in the presence of diarrhea, this is strong presumptive evidence of infection with EPEC. In most adults with EPEC diarrhea, including "turista," the only judicious therapy is: diphenoxylate hydrochloride with atropine sulfate (Lomotil®) 2.5 to 5 mg every six hours but, if the diarrhea is associated with fever and especially severe, with myalgia and profuse cramps, therapy with two grams of ampicillin daily in divided doses may result in a cure in three days. Treatment should start with ampicillin, administered intramuscularly, until the antibiotic sensitivity test is returned. In-hospital pediatric epidemics which at times cause lethal diarrhea may be aborted by therapy with antibiotics to which EPEC are sensitive.

CHARLES CRONIN, MD

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Hemophilus Vaginitis—A Venereal Disease

HEMOPHILUS VAGINALIS has been estimated to be the causative agent in 6 to 52 percent of vaginitis cases, and incidence of this condition seems to be increasing. Diagnosis requires (1) a high index of suspicion, (2) evidence of excess bacteria in a wet smear and (3) vaginal epithelial cells that look semi-opaque with a Sedi® stain or Gram stain, which are referred to as "clue cells." Small Gram-negative bacilli associated with epithelial cells, rather than with leukocytes are noted. Oral contraceptives and intra-uterine devices do not influence the incidence of Hemophilus vaginitis. Sulfa vaginal creams and suppositories used for three weeks result in a 50 percent cure of this problem. However, the author has found that a course of ampicillin 500 mg four times daily for five days has been a much more effective therapeutic agent. Men who have been infected with Hemophilus have also been successfully treated with this method.

BENSON MCGANN, MD

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Santa Barbara

EDITORIAL

Cardiac Valve Replacement

The Rationale for Earlier Operation

During the past decade there has been a progressive reduction in the operative risk of valve replacement, even in patients with far-advanced heart disease. This has given us the opportunity to study the late results in a balanced group of survivors, including many poor-risk patients. As noted by Carey and associates, in this issue of The Western Journal of Medicine, there is a significant late mortality due to progressive heart disease unrelated, for the most part, to specific prosthetic complications. Furthermore, the restoration of satisfactory valve function does not restore the functional Class I or II status to all long-term survivors. On the contrary, many patients who survive for extended periods of time remain significantly limited in exercise tolerance.

The authors rightly feel, in view of these results, that it is proper at this stage in the development of valvular surgery to review our current thinking with regard to the indications for earlier operation. They point out that perhaps the timing of operation should depend upon specific features of the patient's disease that bear on the late results, such as cardiac mass, cardiac dilatation and evidence of ventricular dysfunction—rather than preoperative functional classification.

Our own experience very much supports this view. For mitral valve replacement, for example, the operative mortality for the non-cloth-covered ball-valve prosthetic device (6120) implanted from 1965 to 1968 was 10 percent. With the various cloth-covered mitral prosthetic valves (6310-20-40) implanted from 1968 to the present, the operative mortality is 5 percent in 297 such patients. Late mortality and morbidity is best viewed using an actuarial technique. Relative survival curves can be derived by adjusting the actuarial survival by the expected survival corrected for age and sex. Using this technique in a group of 329 patients with isolated mitral valve replacement surviving operation, including both non-cloth-covered and cloth-covered prosthetic devices, the 5-year relative survival rate is 85 percent, and the 8-year survival rate is 80 percent. Of 24 late deaths in the cloth-covered series, eight were due to arrhythmias or congestive heart failure, and only two were prosthetic-related due to endocarditis. Of 14 deaths in the non-cloth-covered group six were due to congestive failure or arrhythmia, and only four were prosthetic-related (embolism in three, endocarditis in one).

In a report of the University of Oregon Medical School, patients with mitral valve replacement were analyzed by computer, and poor late functional results were clearly related to the duration of disability, the history of previous mitral surgery and the presence of tricuspid regurgitation, rather than to specific complications related to the prosthetic heart valves. However, specific complications must be taken into consideration in weighing the risks of valve replacement against the risks of deferring the operation. Fortunately, with the current generation of cloth-covered mitral prosthetic valves in use since 1968, the actuarial risk at five years of embolus is 3 percent, infection 2 percent, reoperation 4 percent. Thus, operations should be, ideally, performed before disability has been too prolonged, and before functional tricuspid regurgitation has developed. On the basis of this information we currently recommend surgical operation for patients in early functional Class III.

Our results with aortic valve replacement are also similar to the authors', with an operative mortality for the current cloth-covered aortic prosthetic valve (Model 2400) of 5 percent compared to an earlier operative mortality of 12 percent. The late relative survival including all aortic prosthetic valves, both cloth-covered and non-cloth-covered in 437 patients is 75 percent at eight years for males. For females relative survival falls to 94 percent at two years but then rises to approximately 98 percent at eight years. As with mitral replacement congestive heart failure and arrhythmias are the most common causes of late deaths. With cloth-covered valves, for example, only seven of 38 late deaths were prosthetic-related (embolus in five and endocarditis in

two). For patients receiving anticoagulants with cloth-covered aortic prosthetic valves, the actuarial incidence of embolism is zero at five years compared with 18 percent with non-cloth-covered valves (Model 1200-1260). In terms of embolism per 1,000 patient-years of follow-up, there were four episodes for non-cloth-covered prosthetic valves, and ten episodes for cloth-covered in patients not receiving anticoagulant therapy. There were no episodes in 116 patients receiving anticoagulants who had a cloth-covered aortic prosthetic valve in place.

The actuarial incidence of infection is less than 4 percent at five years with cloth-covered valves. Specific complications, such as hemolytic anemia due to cloth tear have produced an actuarial reoperation rate of 8 percent at five years. However, current models of cloth-covered valves containing a track on the inner surface of each strut are free from this complication.

While our computerized review of aortic valve patients is not yet complete, cardiac mass and ventricular function appear to be the important determinants of the quality of life and functional classification after operation. On this basis it is our current policy to recommend valve replacement in Class I patients if there is a striking progression in cardiomegaly in presence of aortic regurgitation.

While medical considerations must play the dominant role in determining the timing of operation for chronic valvular heart disease, we must also consider the chance for social and economic rehabilitation. It has been our experience that patients who have been off work for more than six months before operation have a very poor chance of returning to work postoperatively, even if they have had an excellent physiological result.

Thus, we find ourselves in essential agreement with Carey and his associates. Cardiac valve replacement must be considered earlier in the course of the patient's disease in order to prevent the development of irreversible heart disease. Exactly how early this should be is the problem to be answered by each of us depending upon a balancing of the risks, both early and late, with each patient. The trend toward earlier operation is definitely here, and how far we extend it will depend upon a continuing analysis of the results we achieve.

ALBERT STARR, MD
Professor and Chief
Cardiopulmonary Surgery
University of Oregon Medical School
Portland

WAMI

THE DESIRABILITY of better distribution of health manpower and particularly of physician manpower to underserved areas is widely accepted. Yet the most important action is where there is some density of physicians, other health manpower and health care resources. Many knowledgeable observers feel that there has been and still may be an overall physician shortage. And these are times when an unprecedented number of young Americans are seeking to become physicians, and an unprecedented number of foreign medical graduates are being admitted to this country and given licenses to practice here. And while medical educators are under increasing political pressure to provide educational opportunities for foreign medical graduates, they find themselves without the wherewithal to offer qualified Americans the opportunity to become physicians whether or not they come from medically underserved areas or cultures.

It is against this rather schizophrenic background that a variety of attempts are being made to strengthen health manpower and health care services in deprived or underserved areas. In those instances where major medical centers with a full complement of physicians and resources find themselves in or adjacent to major underserved areas, the effort has often been to develop models for health care delivery in these areas. This has occurred in Boston, Baltimore and Chicago, for example. There have also been delivery models developed in areas quite remote from major medical centers, but these seem to thrive best when they can somehow tap into the resources of a major medical center. Another, quite different and very important approach has been to decentralize medical and health care education to underserved areas. This has the advantage of bringing the educational processes to where the practice needs are and allows improvements in the distribution of health manpower and health care services to flow from this. This approach was pioneered on a national scale by Regional Medical Programs, which emphasized transferring the knowledge

which had been accumulating in the major health science centers out to where the underserved needs were, and some decentralized training of health manpower was a by-product of this. More recently Area Health Education Centers in the model of the Carnegie Report are being tried in several areas of the nation. In this model, major health science centers undertake to carry out training programs for interns and residents in primary care specialties and clinical training for medical students in underserved areas in the expectation of attracting physician manpower to the area and of improving both the quantity and the quality of the services. This model is now being tested, and how successful it will be is not yet known. It is worth noting in passing that in each of these approaches a major health science center, often a university medical center, seems to play a significant if not an essential role.

As reported elsewhere in this issue, the states of Washington, Alaska, Montana and Idaho (WAMI) have now banded together in yet another experiment in bringing medical education to underserved areas. In this model the University of Washington School of Medicine plays the central role and ways have been found to conduct both preclinical and clinical instruction of medical students in underserved areas, yet under the aegis and supervision of the medical school. As the program gets underway it should serve effectively to decentralize a number of aspects of medical education, and so permit a larger number of students to be enrolled. It also should upgrade the quality of care in underserved areas and make practice there more attractive to physicians. And it will certainly provide a better opportunity for young Americans in these areas to embark on a career in medicine. If the program succeeds, the University of Washington will have taken another pioneering step not only in medical education but in identifying a role for a university medical center in helping to overcome some of the problems of physician distribution in underserved areas.

The WAMI project will be watched with interest.

—MSMW

Myelomeningocele

REVOLUTIONARY CHANGES have occurred in the management of myelomeningocele during the past 15 years. This disease is the second most common chronic disabling condition of childhood, occurring with a frequency of about 1 per 800 births. The current concepts and therapeutic recommendations of a group active in this field are presented in this issue.

Basic to rational treatment of any disease is an understanding of its cause, mechanisms and natural history. The cause of myelomeningocele is unknown although it is clearly linked to other neural tube defects and has a familial incidence with about a 5 percent recurrence risk. Studies suggesting a causative link with potato virus need further confirmation.[1]

The embryologic insult occurs early in gestation, probably between the 21st and 28th days and is characterized by leakage of spinal fluid and a discrepancy between growth of mesodermal and ectodermal tissue. If spinal fluid leaks into the amniotic fluid it is detectable by the presence of alpha-fetoprotein. Amniocentesis is recommended for mothers known to be "at risk."[2] A further important concept sometimes not well appreciated is that the neurological lesion is not simply a lower motor neuron lesion. Rather, isolated cord segments may exist producing a mixture of spasticity and flaccidity which affect not only the peripheral muscles but the bladder as well.

Before present-day treatment programs, disability was severe and long-term survival was rare. It remains true that chances for survival past the intrauterine period are limited but the rate of survival from birth to age two is now around 60 percent. Considering the multiple handicaps and hazards of surgical operation and sepsis, this is a remarkable achievement. These children face odds of hydrocephalus in about 75 percent of cases, severe retardation in about 10 percent, urinary tract infection in most and variable degrees of motor dysfunction in nearly all.

Perhaps the most controversial issue in treatment has been whether to do immediate closure or delay this procedure.[3,4] The case for closure within the first 24 hours to prevent further neuro-

logical damage is shaky at best, but closure of the persistent meningocoele is clearly desirable. Surgical correction of a kyphotic deformity at the time of initial closure has proven to have substantial mortality and recurrence risk, yet it may prove justifiable as techniques improve.

Urinary tract failure remains the most common cause of death after infancy. It is now well recognized that only a few children with myelomeningocele have normal bladder function at birth and reflux in the newborn has been reported as high as 25 percent.[5] Reflux in the presence of persistent sepsis may require ileal or colonic loop diversion, improving chances of survival for all and creating an improved social situation for girls.

Management of skeletal deformities has undergone considerable change. Some operative procedures initially greeted with enthusiasm have proved to be of questionable virtue. Multiple fusion procedures in the feet have proved untenable because of trophic ulceration and neuropathic fusion breakdown. The heralded psoas transfer through the ilium to the greater trochanter has been shown to have limited function and has not consistently achieved hip stability.[6] External appliances to control scoliosis have been unsatisfactory, requiring use of both anterior and posterior stabilization procedures on the spine. Newer procedures such as Achilles tenodesis to the fibula to correct calcaneus deformity show promise.[7]

The concept that emerges from the collective experience is that this condition needs to be treated very well or not at all. Surgical procedures are used first to enhance survival and for early control of hydrocephalus. Early detection and treatment of urinary tract sepsis is the next priority. Procedures to produce a straight spine, straight knees and mobile hips and feet follow. The need for these procedures is reasonably predictable so they may be carried out early to allow maximum social and educational opportunities.

Successful treatment demands a multiple discipline approach. The challenge of developing a well-functioning team of specialists, which includes social workers, public health nurses and psychologists as well as physicians, requires a significant commitment of all involved in addition to administrative skill.

In spite of a large collective experience many questions remain unanswered. Treatment programs differ in philosophy and methods, and each center continues to alter its program.

Superimposed on the medical challenges has been the moral issue of whether treatment should be withheld. Sophisticated evaluation of motor, sensory, intellectual and urinary systems in a sick newborn child are impossible. A variety of clues have been used to prognosticate and it is clear that selection is being practiced to varying degrees in all centers dealing with this condition. Considering the advances in management during the past 15 years and the uncertainty of prediction, caution should be exercised in this endeavor to be merciful.

RODNEY K. BEALS, MD
Professor of Orthopedics
University of Oregon Medical School
Portland

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National Health Insurance

An Opportunity for a New Approach

At this writing National Health Insurance (NHI) now seems unlikely to be passed into law by this Congress. It may be significant that even behind closed doors and pressured by its powerful chairman, the Ways and Means Committee did not come together on an NHI bill to place before the House of Representatives at this time. The matter has been under discussion for decades. But somehow the approach used has not yet worked. But if there is in fact a need for some form of NHI, and it is generally believed that there is, then a problem exists which should be solved.

The approach that has been used at the national level appears to be the adversary approach that has now come to characterize so much of the American way of trying to solve problems and disagreements. (This adversary approach is to be

distinguished from the open discussion, open debate and arrival at a consensus which characterizes the democratic process—and is lacking in totalitarian systems.) It is an unfortunate characteristic of the adversary approach that the basic problem tends to be poorly defined, obfuscated, or lost sight of or displaced as the issue becomes converted into a contest between powerful forces, each seeking to impose its will upon the others. Moreover, any compromises which may finally be reached are apt to be less than adequate solutions for the original problem. We see this happening everywhere in our legal and political system and it seems to have been the case with NHI.

If one thinks about it, an approach in which adversaries seek to impose their wills upon one another is actually very poorly adapted to solve the problems of our highly interdependent technologic society with its wide variety of human needs for health, satisfaction and well-being—to say nothing of peace both at home and abroad. Certainly if things are to run smoothly with a minimum of friction, adversary attitudes and behavior seem both impractical and inappropriate. Rather the approach should be more one of common recognition by all concerned of the fact that there is a problem which has arisen and needs to be solved, of the precise nature and definition of this problem and of a common purpose to find a workable solution and to carry it through in a spirit and atmosphere of cooperation and collaboration. This was more easily done in the town meetings which were so much a part of the early history of this nation. NHI is surely a local problem and a national problem, and it surely has many ramifications throughout this highly interdependent technologic society with its wide variety of very personal human needs. And it should be obvious that whatever NHI plan is adopted will need the support and, better yet, the enthusiastic support of all the major elements, both local and national, involved in the delivery of health care, if it ever is to work smoothly and efficiently in practice.

The California Medical Association with its catastrophic Health Insurance Proposal has attempted this kind of a broadly based approach. It does identify a definite problem which pervades the whole of society—the financial ruin caused by catastrophic illness or injury. The proposal to solve this problem was developed by a Task Force which we understand included representatives of many elements of the health care industry which would be involved in implementing the proposal were it to be adopted by the Congress. This seems a reasonable approach, even pervasive in its rationality and emphasis on getting the interests and forces involved together to solve a difficult community and national problem. It seems like an approach that ought to be tried, but it has yet to be given the chance to be tested.

It seems that at the national level at least, the adversary approach is deeply ingrained in the attitudes of almost all of the major elements which will become involved in NHI, and realistically there is small likelihood that this will change. But it might. One can hope that there may be a new attitude of cooperation and collaboration on the part of government and society as a whole toward some of the complex problems of human, technologic, social, economic and political interdependence which now face the nation.

If this should prove to be the case then there could be an entirely new approach to the problem of NHI along the lines that have been suggested here. A more precise definition of exactly the problem to be solved will need to be identified and accepted, and a genuinely new attitude and approach by the federal government, the medical profession and other elements of the health care system will be needed. But this should not be impossible to accomplish. After all, when one gets down to it, it is the "if there is a problem let's get together and solve it" approach that has accomplished so much in this country and made America the great nation it is. It might be worth applying this to the problem of NHI.

—MSMW

CASE REPORTS

Refer to: Connett MC: An anatomical basis for unilateral leg edema in adolescent girls. West J Med 121:324-326, Oct 1974

An Anatomical Basis for Unilateral Leg Edema in Adolescent Girls

MAHLON C. CONNETT, MD
Concord, California

EDEMA OF THE LOWER EXTREMITIES, particularly in female patients, has traditionally been associated with lymphatic disease.[1,2] From a survey of the modern medical literature it appeared that iliac vein obstruction in the young has not been recognized as an etiologic factor in the development of relative enlargement of the left lower extremity. Three cases are presented in which relative enlargement of the left leg was the presenting complaint, all in adolescent girls. In each case narrowing or obstruction of the common iliac vein on the left side was documented by a phlebogram as well as by intraoperative findings.

Reports of Cases

CASE 1. A 15-year-old girl was first seen and examined by me in 1966 at the age of 8 years. At that time the parents said that the patient's left leg seemed bigger around than the right, and this was confirmed at physical examination.

The patient was observed to be rather thin. The blood pressure was 110/70 mm of mercury and the pulse rate 72. The circumference of the left leg was greater than the right. Pitting edema was not present. Measurements, in inches, were as follows:

	Circumference	
	Right	*Left*
Mid-thigh	18¾	18¾
Calf	12¾	13
Ankle	7⅞	8

Submitted February 20, 1974.

Reprint requests to: M. C. Connett, MD, 2425 East Street, Concord, CA 94520.

Figure 1.—Left saphenofemoral phlebogram, Case 1.

The patient was treated with an elastic stocking and was observed at regular intervals until her growth was complete. Phlebograms were obtained in 1966 and were repeated in 1973 (Figure 1). The findings of both phlebograms were similar—namely, an occlusion of the left common iliac vein at its junction with the vena cava. When the patient had reached full growth, operation was carried out. After the exposure of the retroperitoneum, occlusion of the left common iliac vein by a congenital band at the take-off point of the right common iliac artery was noted. A band from the prevertebral fascia could be identified and was removed (Figure 2). The left iliac vein was approximately four times the size of the right common iliac vein. After removal of the congenital band the veins quickly became equal in size.

The postoperative course was uneventful. Postoperative leg measurements are not available.

CASE 2. A 16-year-old girl was examined because of "swelling" of the left leg over a four-year period. There was no history of trauma or inflammation.

On physical examination the blood pressure was 120/70 mm of mercury and the only physical abnormality noted was gross difference in size between the left leg and the right. There was no pitting edema. Measurements, in inches, were:

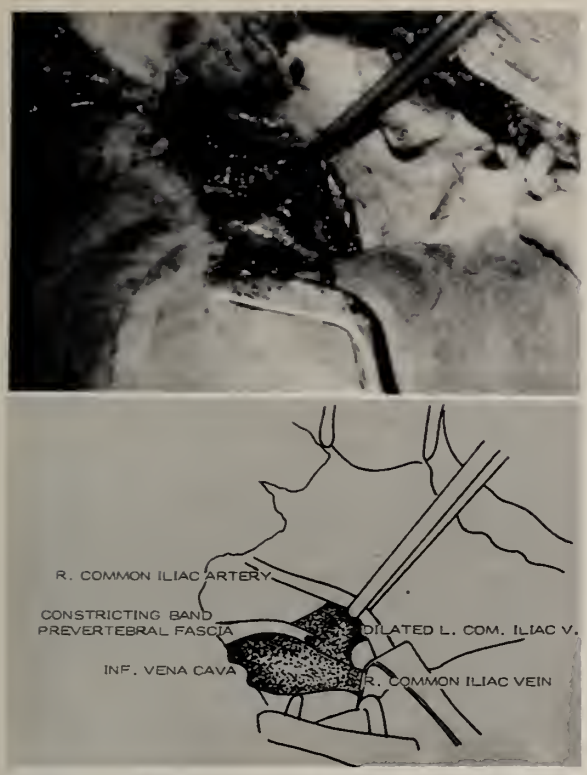


Figure 2.—Pathologic changes seen at operation in Case 1.

	Circumference	
	Right	*Left*
Mid-thigh	21	21
Calf	13¼	14¼
Ankle	7½	7¾

Phlebograms revealed obstruction of the left common iliac vein at its junction with the vena cava, with an abundant collateral flow (Figure 3).

At operation, the retroperitoneum was mobilized. A band was found across the common iliac vein on the left side at its junction with the vena cava. The left iliac vein was three or four times the size of the right. A band from the prevertebral fascia was found and removed. The left iliac vein rapidly diminished in size to that of the right. The postoperative course was uneventful.

Measurements of the lower extremities six months after operation were as follows (in inches):

	Circumference	
	Right	*Left*
Mid-thigh	19	19
Calf	12½	13¼
Ankle	8	7½

Later the legs became equal in size.

Figure 3.—Left saphenofemoral phlebogram, Case 2.

CASE 3. A 19-year-old girl was examined because of swelling of the left leg. At age 16 she had had an episode of phlebitis involving the calf of the left leg, and anticoagulant therapy had been given.

On physical examination in the present instance the blood pressure was 110/70 mm of mercury. There was some obvious disparity in the size of the legs. The measurements, in inches, were:

	Circumference	
	Right	*Left*
Mid-thigh	18	18½
Calf	13	13
Ankle	8¼	8¾

A phlebogram showed a point of occlusion and then a space in which the left common iliac system was not visualized, with an abundant collateral circulation (Figure 4).

At operation, after exploration of the retroperitoneum, a point of compression of the common iliac vein on the left was observed, and a fibrous band from the prevertebral fascia was found and removed. The common iliac vein was opened, and

Figure 4.—Left saphenofemoral phlebogram, Case 3.

it was found that there was no communication between it and the vena cava due to agglutination of the anterior and posterior walls at the junction of the two vessels. The iliac system was patent in small segments down to the inguinal ligament. The common femoral vein was patent, and there was abundant collateral circulation through the ovarian vein and pelvis. Because of the unusual length of the involved segment, reconstruction of the iliac system was not possible.

Discussion

The features observed on phlebograms were similar in all three cases; and in each of them an anatomical variant, a band occluding the left common iliac vein at its junction with the vena cava, was observed at surgical exposure. It would appear that the first two cases may have represented earlier phases of a more complex syndrome seen in the third case. In the first two cases the increased venous pressure and relative stasis of the venous system in the left leg were readily treated by removing the congenital band and mobilizing the aorta and the right common iliac artery. As to the third case, one must wonder whether the left common iliac system was ever patent. With the absence of any inflammatory reaction or findings compatible with phlebitis of the iliac system on the left side, it appears that a reasonable speculation would be that the congenital band obstructing the left common iliac vein eventually was responsible for nonfunction of the iliac system on that side.

In all of these cases there was only modest enlargement of the left leg, which is consistent with the knowledge that venous occlusion produces far less edema than lymphatic occlusion. The massive edema associated with the postphlebitic syndrome is considered to be caused by secondary lymphangitis.

No previous report of the gross pathologic changes observed in these three cases could be found in the literature. Since it is improbable that these were simply isolated instances in a relatively small community, it is possible that the condition is more widespread but not recognized. Whether or not it is significant that all the patients were young women can only be conjectured.

Any stasis in the venous system would preclude the development of phlebitis. More pertinent, interruption of common iliac venous flow may be conducive to iliofemoral venous thrombosis.

Diagnosis of the condition can be made readily by phlebography, as is particularly illustrated in Figure 3, which plainly shows the band or the occlusion of the left common iliac vein. Since phlebography can be done with relatively little risk, it may be considered a primary diagnostic procedure in patients with obscure minor disparities in leg size.

Summary

Obstruction of the left common iliac vein due to a congenital band formed by the prevertebral fascia was observed in three cases. Diagnostic features, pathological changes and surgical treatment are discussed, as well as possible implication of the development of thrombophlebitis.

REFERENCES

1. Allen EV, Barker NW, Hines EA Jr: Peripheral Vascular Disease. Philadelphia, W. B. Saunders Company, 1958
2. Haller JA Jr: Deep Thrombophlebitis. Philadelphia, W. B. Saunders Company, 1974

LETTERS *to the Editor*

A Simple Kit for Travel

To the Editor: Members of the California Aviation Safety Council believe that physicians travelling by plane should carry with them a simple kit for the treatment of themselves or fellow passengers in event they become ill while aloft.

The drugs and equipment needed for this purpose can be carried in a flat cardboard box of good quality (a sample box will serve well) approximately 9½ × 5 × 1 inches. To avoid difficulties with custom clearance on international flights, the name of the physician should be shown on the cover, and inside the box there should be a typed list of the contents and a statement that they are for the personal use of the physician, his family and possibly for emergency treatment of others.

I tested the customs clearance by showing my kit at the customs office at my point of departure from the United States, where I was told that in the amounts listed, the drugs would cause no problems. And I had no difficulties at any of the points at which I passed through customs offices —in Germany, Austria, Switzerland, and on my return to the United States.

The box I use is light, can be slipped into a carry-on tote bag and can be opened easily for customs inspection. Its contents—peculiar to my needs but also generally useful—are listed in the table.

Wayne P. Chesbro, MD
Chairman, California Aviation Safety Council
Berkeley

Drug	*Generic Name and Dosage*	*Quantity*
Demerol®	meperidine hydrochloride, USP, 50 mg per ml in 1 ml ampules	4
Plastic Syringes (Disposable) with Needles	3 ml (cc), 25 Gauge, ⅝"	4
Nembutal® Suppositories	sodium pentobarbital 200 mg	3
Antivert®, or preferably Antivert®/25 Chewable	meclizine 25 mg	12
Keflex®	cephalexin monohydrate 250 mg	32
Lanoxin®	digoxin (Digitalis lanata) 0.25 mg	24
Compazine® Spansule®	prochlorperazine 15 mg	4
Nitrostat®	nitroglycerin 0.6 mg	24
Empirin® Compound	acetylsalicylic acid 230 mg, phenacetin 150 mg, caffein 30 mg	12
Empirin® Compound with Codeine, No. 3	codeine 30 mg, plus Empirin® Compound	6
Donnazyme® Tablets	hyoscyamine sulfate 0.0518 mg, atropine sulfate 0.0097 mg, hyoscine hydrobromide 0.0033 mg, phenobarbital [⅛ Grain] 8.1 mg, pepsin NF equivalent 150 mg, pancreatin NF equivalent 300 mg, bile salts 150 mg	6
Lomotil®	diphenoxylate hydrochloride 2.5 mg, atropine sulfate 0.025 mg	36
Co-Pyronil®	methapyriline hydrochloride 25 mg, pyrrobutamine phosphate 15 mg, cyclopentamine hydrochloride 12.5 mg	12
Visine® Eye Drops	tetrahydrozoline hydrochloride 0.05%, sodium chloride, boric acid, sodium borate, with benzalkonium chloride 0.01% and disodium ethylene diamine tetraacetate 0.1% added as preservatives	1 Bottle
Absorbent Cotton Balls		10
Band-Aids®		12

Thermography to Localize Parathyroid Adenoma

To the Editor: The recent article by Smith and Usselman (Wasson III EC, Smith JL, Usselman JA: Localization of a parathyroid adenoma by thermography. West J Med 121:144-146, Aug 1974) is of considerable interest.

In our experience we have successfully localized three parathyroid adenomas on three patients who had a biochemical pattern of parathyroid hyperfunction.

One word of caution that we would like to bring to the attention of thermography enthusiasts is the fact that occasionally, especially in men, one can find areas of increased temperature in the general central area of the neck where the thyroid and parathyroids would be. These areas of increased temperature are probably related to minor injuries, folliculitis or the trauma of shaving. For this reason we have elected to extend our time of observation when we do thermography for localization of parathyroid adenomas. What we do, after the initial study where we find an abnormality, is to ask the patient to come back a week or two later and repeat the study. If the area of increased temperature is persistently the same without change and we cannot palpably or by observation of the skin find any evidence of skin abnormality, we consider this to be a truly abnormal reading.

Jorge A. Franco, MD
San Jose

Permanent Acupuncture Needles

To the Editor: I was interested indeed to read in the August 1974 issue, "Case Reports," the article [on acupuncture needles] by Doctors Behrstock and Petrakis [Behrstock BB, Petrakis NL: Permanent subcutaneous gold acupuncture needles. West J Med 121:140-141, Aug 1974].

Permanent acupuncture needles need not be gold, as they have pointed out. When I was working in Indonesia in 1964, I saw many patients, including a number of children, who had acupuncture needles in their bodies which showed up on x-ray studies. I noted this particularly in some children who had severe urinary infections with vesicoureteral reflux, which apparently had been treated unsuccessfully by acupuncture.

Willard E. Goodwin, MD
Los Angeles

Critical Masses in Health Care

To the Editor: Your concept of critical masses in the distribution of health care services is interesting [Critical masses in the distribution of health care services (Editorial). West J Med 121: 136-137, Aug 1974], and I believe essential to effective planning.

I would like to offer one suggestion for the planners. They might well abandon the concepts which certainly appear to be invalid, and concentrate on concepts involving modern communication and transportation. Certainly the Armed Services have demonstrated that excellent care can be provided even though sick and injured must be transported long distances. The basic concept is to bring the patient to where the doctors are, rather than the doctors to the sparsely settled rural areas and dangerous ghettos. I am convinced that the concept is feasible and believe that if the time, energy, and funds which have been devoted to invalid concepts were made available, it could be accomplished very quickly.

Marvin J. Shapiro, MD
Encino, California

Tick-borne Diseases

To the Editor: In connection with the article on tick paralysis [Emmons RW, Brewster FM, Nelson BC: Tick-bite in Oregon: Paralysis in California. West J Med 121:142-143, Aug 1974], the enclosed table of diseases transmitted by tick bites in the United States may be of interest to your readers (table adapted from Szalay[1]).

Tick-borne Diseases[1]

Disease	*Infectious Agent*
Tick-borne typhus e.g. Rocky Mountain spotted fever; Q fever	Rickettsia
Colorado tick fever	Virus
Relapsing fever	Spirochete
Tularemia	Bacillus
Babesiosis	Intracellular RBC parasite
Tick paralysis	Tick toxin
Powassan virus encephalitis	Virus

Glenn C. Szalay, MD
Harbor City, California

REFERENCE

1. Szalay GC: Tick-borne disease. Am J Dis Child 127:909, Jun 1974

Trauma Rounds

Chief Discussant
WALTER BALLINGER, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Ballinger W: Management of liver trauma (Trauma Rounds). West J Med 121:329-332, Oct 1974

Management of Liver Trauma

JOHN WILSON, MD:* The Trauma Service would like to present two cases of liver injury today. The first patient was a 19-year-old student, a young man who was involved in a motor vehicle accident while driving without a seat belt. Thrown against the steering wheel of the car, he received blunt trauma to the chest and abdomen. When admitted to the emergency room 15 minutes after the accident, the patient was alert and conscious, with complaint of pain in the right upper quadrant of the abdomen. Blood pressure was 170/78 mm of mercury. The patient had no difficulty in breathing. On physical examination, the abdomen was flat and minimally tender in the right upper quadrant and the epigastrium. Multiple superficial lacerations of the head and neck were noted. The hematocrit was 42 and the urine was clear. Results of neurological examination were within normal limits.

The patient's condition was felt to be stable but in the course of x-ray evaluation he sat up for a chest film and the blood pressure fell to 66 mm of mercury systolic. A saphenous vein cutdown was added to an earlier cutdown in the antecubital fossa. After administration of two liters of Ringer's lactate solution, the blood pressure rose to 90/70 mm of mercury. The patient was taken to the operating room for exploratory laparotomy.

The second patient was a 32-year-old woman who fell down several flights of stairs two days before admission. She noticed malaise, loss of appetite, nausea and vomiting on the day following injury. Two days later she was admitted to the San Francisco General Hospital. Her blood pressure was 170/110 mm of mercury and the pulse 88. On physical examination, increased abdominal girth and abdominal tenderness were noted. The hematocrit was 17. She was taken to surgery shortly after admission.

JOHN KNUDSON, MD:† At laparotomy, in the first patient, approximately 1,500 ml of blood was present in the peritoneal cavity. There was a through-and-through laceration of the liver, passing obliquely upward from the falciform ligament to the vena cava at the level of the diaphragm (Figure 1). There was active bleeding from this site and each attempt to retract the liver resulted in a major gush of blood. By judicious placement of a pack, bleeding was controlled. Fluids were administered rapidly by the anesthesiologist and normal blood pressure was restored. A modified left lobectomy was done to expose the area of bleeding. Bleeding was found to originate for the

*Trauma Service Intern.

Sponsored by the American College of Surgeons Northern California Trauma Committee. Supported in part by USPHS Grant No. GM18470.

Reprint requests to: D. D. Trunkey, MD, University of California Service, San Francisco General Hospital, San Francisco, CA 94110.

†Chief Resident, Trauma Service.

Figure 1.—The liver injury in patient 1, showing avulsion of the left hepatic vein from the inferior vena cava.

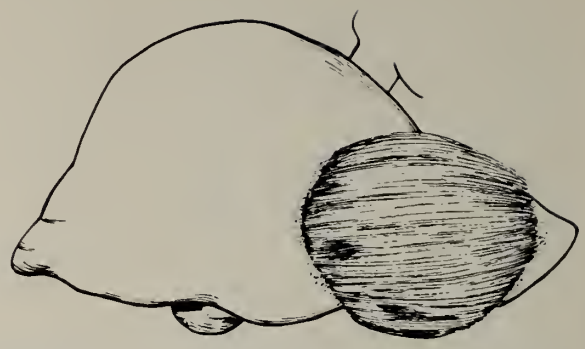


Figure 2.—A large subcapsular hematoma found in patient 2.

most part from the left hepatic vein where it was torn from the vena cava. Once the hepatic resection was completed, exposure of the inferior vena cava was possible, permitting repair of the hole in the vessel. The middle hepatic vein, which communicated with the left hepatic vein, was ligated. Further hemostasis was carried out by suture ligature of bleeding points in the raw surface of the liver. The hepatogastric ligament was sutured so as to cover the raw surface of the liver.

The second patient was originally thought to have had rupture of the spleen but at operation a large subcapsular hematoma (Figure 2) was found. Approximately 1,000 ml of blood was present in the peritoneal cavity. The hematoma was an inch thick and covered the entire left lobe, centering on the falciform ligament. The liver capsule was removed, revealing a deep laceration of the left lobe of the liver. The lateral lobe was resected. Hemostasis was difficult because of continued oozing from the raw surface of the liver. Large Penrose drains were placed before the abdomen was closed.

F. William Blaisdell, MD:* *Did you use any kind of hematologic support in these patients?*

Dr. Knudson: The second patient was never in shock, and blood loss preceded operation by several days. Bleeding from the Penrose drains stopped spontaneously soon after the abdominal closure. The young man required 14 units of blood during operation. We gave him fresh frozen plasma and platelet transfusion, in addition to blood, in anticipation of bleeding problems and this apparently prevented any bleeding difficulties. We re-explored the next day because we were concerned about the viability of the liver. On re-exploration, the liver looked satisfactory and the abdomen was dry.

Dr. Blaisdell: *I would like to introduce our department's visiting professor of surgery, Dr. Walter Ballinger. Dr. Ballinger is Bixby Professor of Surgery at Washington University, St. Louis, and he has written extensively on trauma. Dr. Ballinger, would you please use these cases as a basis for discussing the management of liver injuries?*

Dr. Ballinger: These problems show that we can have delayed manifestation of liver injury and how subtle these injuries can be. The management of liver trauma has swung progressively from ultraconservative to ultraradical and is now swinging back toward middle ground. We are attempting to differentiate between various types of liver injuries and to apply specific treatment for each. Liver resection should not be necessary in more than 5 percent of all liver injuries.

The basic questions are when to drain, when should the liver laceration be oversewn and what are the indications for resection? Most liver lacerations are superficial injuries, and undoubtedly a good number are never diagnosed or treated specifically. The amount of bleeding is at most several hundred milliliters. These superficial lacerations should simply be cleaned up and the liver carefully assessed. No attempt should be made to close them, and after peritoneal toilet is completed, drains should be placed in the vicinity of the laceration and the subhepatic space and the abdomen then closed.

If the laceration is still bleeding at the time of laparotomy, the depth of the laceration should be investigated and bleeding points secured by suture ligature. With good light and suction, combined

*Chief of the Surgical Service at San Francisco General Hospital and Professor of Surgery, University of California, San Francisco.

with an arterial clamp placed temporarily on the portal triad, the area can be cleaned up so the bleeding point can be seen and secured. These deep lacerations should not be closed but rather left open to drain. The use of deep mattress sutures is to be decried because they either compromise more liver anatomy or produce a closed space in the liver. This sets the stage for hematobilia and liver abscess.

Most deep lacerations can be controlled conservatively and unless there has been major avulsion of the liver or devascularization of a lobe or segment, we would attempt to avoid resection if at all possible. For the type of injuries presented here today, there is no question that circumstances dictated resection. The first case was a real challenge because the left hepatic vein was avulsed from the vena cava. This patient was particularly lucky to have been treated here. Most such patients are dead by the time they reach the operating room. Even if they live long enough for laparotomy to be done, there is great difficulty in controlling the hemorrhage. We have yet to save a patient who has significant avulsion of hepatic vein from the vena cava. We have not been able to use the bypass which permits isolation of injuries of this type. The injury in the first case was the most serious kind of liver damage a person can have. The surgeon must know his anatomy well to avoid compromising all of the hepatic venous drainage.

The second patient was much less of a problem. She clearly benefited from the left lateral lobectomy, which is the easiest type of resection to do.

Nothing is more important than the decision to re-explore when the viability of the liver is questionable or when initial control of bleeding is not adequate.

Despite the negative findings at re-operation in the first patient, the nature of the injury was such that I think the decision was the proper one.

DR. BLAISDELL: *Dr. Ballinger, would you comment on the use of common duct drainage in liver injury?*

DR. BALLINGER: In the past we did use T-tubes more or less routinely. The studies by Lucas in Detroit tend to indicate there is more risk than benefit in the use of T-tubes. I would not abandon the use of the T-tube completely, but I would use it only on those infrequent occasions when there is a complicated injury and when I might wish to evaluate the liver postoperatively with cholangiography.

DR. BLAISDELL: *Dr. Ballinger, do you have any specific comments on subcapsular hematoma?*

DR. BALLINGER: Many people have the opinion that subcapsular hematoma is a relatively benign lesion. The second case is a good example of how the liver can be crushed by a blunt traumatic injury and yet the capsule remain intact. The intact capsule and hematoma obscure the real extent of the injury which may lead to delayed rupture and, of course, intrahepatic abscess. When you see a subcapsular hematoma, there is probability of a serious disruption of liver substance underneath the hematoma. Therefore, the capsule should be opened and the hematoma cleaned out. Any bleeding vessels should be ligated in the depth of the laceration, or resection done if the liver is badly traumatized.

DR. BLAISDELL: *Dr. Ballinger, we would like to get your comments about the postoperative management of these patients.*

DR. BALLINGER: *How long was the clamp on the portal triad?*

DR. KNUDSON: About twenty minutes.

DR. BALLINGER: What we are balancing is the condition of the liver, versus the ischemic time, versus the temperature. The question is how adequate is the reserve of the liver that we are going to leave behind? All these variables have to be taken into consideration. If I were dealing with an older patient with a complicated injury, I would probably try to use icewater lavage in an attempt to get some protection and decrease ischemic damage. In these circumstances, it is possible to lengthen ischemic time from about thirty minutes to perhaps forty-five minutes or an hour. When we are dealing with young patients such as those presented here, whose livers are in good shape, we probably would not be concerned about ischemic damage in the postoperative period.

When you have hepatic venous disruption, it is mandatory to ensure adequate exposure. Can you describe the incision used in the first case?

DR. KNUDSON: Initially, we made a midline incision. When the difficult nature of the injury was recognized, we did carry the incision into the chest with a median sternotomy. After cutting the fibers of the diaphragm, we had excellent exposure.

DR. BALLINGER: *I would like to ask what your experience with the total hepatic bypass has been, Dr. Blaisdell?*

DR. BLAISDELL: We have used this now in approximately 12 instances and have three survivors of suprarenal vena cava injury or hepatic vein avulsion. One of the problems is that by the time you are mentally prepared to use it, the patient has exsanguinated. We still favor cannulating the left atrium but the inferior vena cava route can be used. Approximately fifteen survivors have been reported in whom a vena cava shunt was used with complete vascular isolation of the liver.

ROBERT C. LIM, JR., MD:* *I'd like to ask Dr. Ballinger if he has any experience with hepatic artery ligation.*

DR. BALLINGER: One of the important advances made by Mays has been to show that hepatic artery ligation can be used selectively in certain cases of trauma to the liver. It offers promise of being of greatest value in penetrating injuries—in those in which there has not been much damage to liver substance but which may produce hemorrhage which is difficult to control. In these circumstances, selective ligation of a hepatic lobar artery may permit control without having to carry out a major resection.

DR. LIM: We have used hepatic ligation in seven patients. At various times, we have ligated the hepatic lobar arteries, the proper hepatic artery and the common hepatic artery. In the latter two instances, it is important not to damage collateral flow. All of our morbidity from hepatic artery ligation has occurred in patients who had mobilization of the liver with corresponding obstruction of capsular collaterals.

We have done laboratory experiments in which xenon clearance studies showed that glucagon augments liver blood flow. As a result, we use glucagon to support the liver until collateral flow improves. We give this in doses of 2 mg intravenously every four to six hours. This is particularly of value to patients in whom we ligate the hepatic artery for bleeding or in whom extensive resection has been done.

DR. BALLINGER: Another advantage of glucagon is that it has a favorable effect on the heart and improves cardiac output.

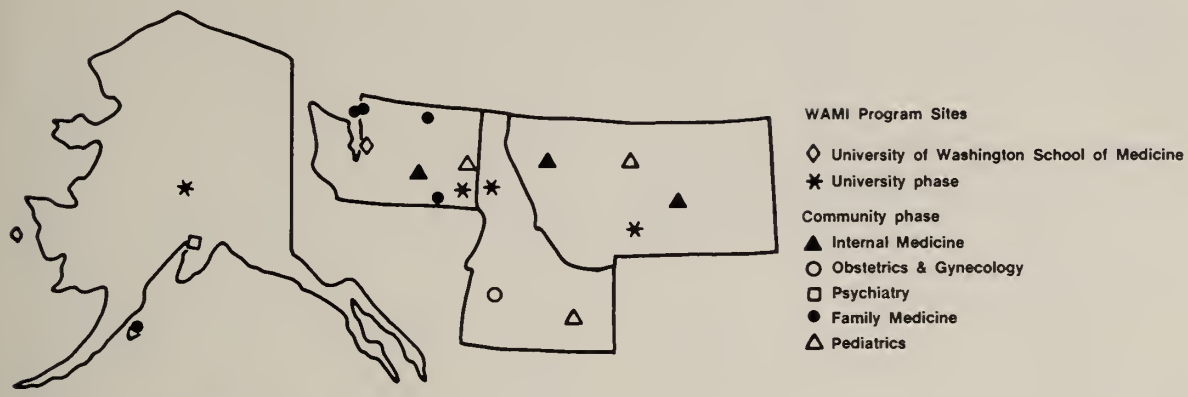
DR. BLAISDELL: *Dr. Ballinger, do you have any strong feelings about how the drainage should be carried out?*

DR. BALLINGER: We would err on the side of putting in too many drains in too many places. We would like to drain the suprahepatic space, the infrahepatic space and the area of the laceration. The drain should not be put into the liver laceration but adjacent to it. Then a good-sized opening should be made in the abdominal wall in as dependent a position as possible and the drains brought through. Ordinarily, we would just use regular Penrose drains, although a sump drain might be of value in selected patients with complicated injuries.

DR. BLAISDELL: Dr. Ballinger, we wish to thank you for a very informative session. I would like to summarize the main points you stressed today —all of which I agree with completely. Most liver injuries can be managed by conservative means. Liver resection can be avoided in all but perhaps 5 percent of liver injuries. It should be reserved for major devitalizing injuries or injuries involving hepatic veins and when there are no alternative means to control bleeding. The bleeding from most lacerations has stopped by the time exploration is done, or it can be controlled by suture ligature of the bleeding points. Through-and-through mattress sutures should be avoided because they devitalize liver tissue or create a dead space which sets the stage for abscess formation or complications such as hematobilia. Good drainage of liver lacerations is essential and this should be dependent so that a large opening can be made in the abdominal wall without danger of evisceration. Selective ligation of a lobar artery or, if necessary, of the common or proper hepatic artery, can be used in instances when there is major inaccessible bleeding. This can be accomplished with less risk than major lobar resection.

*Associate Professor of Surgery, University of California, San Francisco.

Refer to: Schwarz MR: WAMI—An experiment in regional medical education (Medical Education). West J Med 121: 333-341, Oct 1974



WAMI—*An Experiment in Regional Medical Education*

M. ROY SCHWARZ, MD, *Seattle*

The WAMI Territory

The WAMI territory is located in the northwestern portion of the United States and comprises four states or 22 percent of the land mass of the United States. Covering six time zones and containing slightly more than six million people, the states of Washington, Alaska, Montana and Idaho (hence, the acronym WAMI) are, in the main, a sparsely populated, rural region which affords innumerable outdoor recreational opportunities. Rich in natural resources and agriculture, the WAMI territory nevertheless faces serious challenges in the fields of health care and health education.

The author is Associate Dean for Academic Affairs, University of Washington School of Medicine and Director, WAMI Program.

The founders of the WAMI concept included, besides the author, August G. Swanson, MD, presently Director, Academic Affairs, Association of American Medical Colleges, Washington, DC; and John N. Lein, MD, Associate Dean for Continuing Education, University of Washington School of Medicine.

This program was supported in part by The Commonwealth Fund of New York City, and by NIH Contract No. 72-4240, USPHS, HEW.

Submitted, revised, August 27, 1974.

Reprint requests to: M. R. Schwarz, MD, Office of the Dean SC-64, University of Washington School of Medicine, Seattle, WA 98195.

The Challenges

What are the challenges for health professionals in the WAMI territory?

Shortage and Maldistribution of Physicians

While there is considerable disagreement as to the number of physicians necessary for high quality medical care, there does appear to be a shortage and serious maldistribution of certain kinds of physicians in the WAMI territory. Employing the MD to population ratio as a measure, it is apparent that the WAMI states have fewer physicians per unit population than the national average (Table 1). Furthermore, within a given state this ratio may vary considerably as exemplified by the nine counties in the WAMI territory that are without a physician.

A critical appraisal of the types of physicians in the region[1] leads to the conclusion that there are too few physicians delivering primary care (Table 2). Assuming a 4 percent attrition rate, it will be necessary to add 73 family or general practitioners per year to maintain the present

TABLE 1.—*MD to Population Ratio in 1973*

	*MD to Population Ratio**	*MDs per 100M Population†*
United States	1:565	170
Washington	1:556	170
Alaska	1:866	114
Montana	1:930	115
Idaho	1:950	104

*Data obtained from the following sources: Washington State Medical Education and Research Foundation Data Bank, April, 1973; Office of Program Planning and Fiscal Management, State of Washington, April, 1972; Annual Directory of Physicians in Alaska, 1973; Rocky Mountain Medical Journal Directory of Physicians, 1973; United States Census Report, 1970; Idaho Medical Association Directory, 1973. Alaska figures exclude military and Public Health physicians.

†Data obtained from the AMA, 1973.

number of physicians without affecting the present deficit.[2]

Access to Medical Education

From 1963 to 1973 the number of students applying for admission to medical schools in the United States rose from 17,668 to 36,135 (110 percent) and the number of positions in medical schools increased from 9,063 to 14,124 (55 percent). This national phenomenon has been nowhere better exemplified than at the University of Washington School of Medicine (UWSM). As Table 3 indicates, in the 1963 to 1973 10-year period, the number of students from the WAMI territory applying to UWSM has risen 155 percent. In the same 10-year period, the number of positions at UWSM increased from 75 to 125 (67 percent). As a result of this "crunch," competition for admission to medical school has become exceedingly keen. This is especially critical for schools in the West that are expected to educate not only the residents from their own states, but also students who are residents from states without medical schools, including Alaska, Montana and Idaho (the AMI states). As the size of the applicant pool increases, state-supported medical schools can expect progressively greater pressure to admit only residents from their own state. As a consequence of such pressure, residents from the AMI states may expect progressively greater difficulty in being admitted to medical schools.

Demand for Medical Education

Coincidental with the increased demands for undergraduate medical education and the growing class size have come additional demands on medical schools for continuing medical education (CME). These latter demands can be expected to increase for two reasons. First, the possibility of professional recertification will require a more formal emphasis on CME. Second, the establishment of Professional Standards Review Organizations (PSRO), which will review the quality of care being delivered, should define the educational requirements to bring the care to predefined levels. Among these needs will be (a) the education of medical school students, residents and physicians concerning Patient Care Appraisal (PCA), a system of medical audit, how it is implemented and how it can improve the quality of medical care; (b) the development of educational courses designed to correct deficiencies defined by PCA and (c) a more formal emphasis on lifelong learning by the physician. In the Pacific Northwest and Alaska, these needs are especially challenging because of the large geographical areas involved and the absence of medical schools in Alaska, Montana and Idaho.

Patients for Medical Training

Over the past decade, the size of medical school classes at UWSM has increased significantly. This increase has placed a significant burden on the patient resources available for clinical training in Seattle.

Costs of Medical Education

Available evidence strongly suggests a progressively greater preoccupation and concern with the costs of medical education. Recently, studies on the costs of medical education were published by the Association of American Medical Colleges (AAMC) and the Institute of Medicine (IOM). The former study reported an average instructional cost of $8,600 per student per year (range $5,700 to $10,200) while the IOM study indicated a net average educational expenditure of $9,700 (range $5,150 to $14,150).

Since the early 1950's, the Western Interstate Commission on Higher Education (WICHE) has facilitated the transfer of funds from states without medical education programs to states with medical schools in return for the admission of residents. In view of the cost studies referred to, it is apparent that the $5,000 per year supplied by the sending state is significantly less than the costs of medical education. In addition, Deans for Admissions at state-supported medical schools in the West have indicated that this cost-sharing arrangement no longer has a significant influence on the admissions process. It is reasonable to con-

TABLE 2.—*Number of Family and General Physicians in the WAMI Territory*

State	Population	Number MD Family or General Practitioners*	Number Osteopathic Family or General Practitioners†	Total Number MD and DO Family or General Practitioners	Actual Number Family or General Practitioners Required‡	Number Additional Family or General Practitioners Required Per Year§
Washington	3,464,900	1,072	158	1,230	1,386	49
Alaska	317,500	71	3	74	127	3
Montana	713,600	229	32	252	285	10
Idaho	739,600	254	20	274	296	11

*From American Medical Association figures as of December 31, 1972.
†From American Osteopathic Association figures as of December 31, 1971.
‡Assumes one family or general practitioner is desirable per 2,500 people.[2]
§Assumes an attrition rate of 4 percent per year.[2]

TABLE 3.—*Applications for Admission to University of Washington School of Medicine*

Residence	1963	1973	Percent Increase
Washington	180	461	156
Alaska	5	31	520
Montana	40	93	132.5
Idaho	34	76	123.5
TOTALS	259	661	155

clude, therefore, that unless a new arrangement is forthcoming, state-supported medical schools may be forced to reduce greatly, if not eliminate enrollment of residents from states other than the one supporting the medical school.

It is also apparent that the legislature in a state without a medical school would be reluctant to spend the entire cost of medical education for their residents outside of their state. On the other hand, it is generally accepted that the amount of capital and operating costs necessary for a medical school argues against the development of medical schools in the states of Alaska, Montana and Idaho.

The WAMI Program

To meet these challenges, the University of Washington School of Medicine in 1971 embarked upon an experiment in decentralized medical education. The WAMI program, as it is called, has a number of specific objectives.

- Improve the health of citizens in WAMI states through decentralized medical education.
- Increase the number of positions in medical schools without major capital construction.
- Increase the number of primary care physicians in the WAMI states.
- Correct the maldistribution of physicians in the WAMI region.
- Broaden the educational experience of future physicians through the use of clinical resources in communities.
- Improve and expand continuing education programs for physicians and other health care professionals throughout the WAMI region and integrate these programs into an overall plan which includes undergraduate and residency training.
- Expand the financial base for medical education by encouraging all states to pay the full costs of educating their residents.
- Assist adjacent states with the development of medical and other health professional education.

The WAMI Concept

The WAMI concept consists of two separate phases. In the first or *university phase* of the WAMI program, students receive the first year of medical school training at the University of Alaska, Washington State University, the University of Idaho, Montana State University or the University of Washington School of Medicine. For this portion of the curriculum, faculties and facilities already in existence are used. Existing courses at the cooperating universities have sufficed in some cases, while in others, new courses have been developed. By decreasing the burden on the resources in Seattle during the first year, it is hoped that the number of students admitted to medical school can be increased.

This plan is consistent with the medical school curriculum which was adopted at the University of Washington in 1968. The curriculum change emphasized an integration of the basic and clinical sciences, stressed flexible career choices at an earlier time in medical education, allowed for graduation in three years and established a Department of Family Medicine.

It was anticipated that following the experience at these universities, the students would join the portion of the class that began in Seattle for the second year of medical education.

At the conclusion of the basic curriculum, the students enter the elective phase of their education which is predominantly clinical in nature. Under the WAMI concept, students during the elective period would receive a portion of their training at the University of Washington School of Medicine and a portion from physicians in communities of the four-state region *(community phase)*. These community centers of medical education, or community clinical units, have been established in those disciplines for which there is a need and in which the physician manpower is currently maldistributed. Included in this category are family medicine, internal medicine, psychiatry, pediatrics and obstetrics and gynecology. It was anticipated that these units could be used for a portion of the residency training in the discipline for which they were established. Since the greatest need of the WAMI region is (and was) for family physicians to practice in rural parts of the WAMI region, the first of the community clinical units were to be established in family medicine in rural communities. Finally, the units provide access to a patient population for instruction which is not presently available in the University of Washington affiliated hospitals.

From the beginning of the planning, it was anticipated that if practicing physicians were to be involved in the community clinical units, they would be required either to increase the number of hours they work or to reduce the scope of their practice. In either situation, these community teachers would require reimbursement for their educational effort. While some are willing and able to participate, others find it impossible to do so and still supply the health care needs of the community.

In addition, it is generally accepted that residents tend to practice in the area where they received their training. It was anticipated that residents would not only reduce the physicians' burden of instruction for the undergraduate medical students and consequently free the physician for more paient care, but would also allow the resident firsthand experience in how his or her discipline is practiced in a community setting. If the resident was accompanied by spouse and children, they too could become involved in the community and gain an appreciation of the life a physician leads in that community. It was hoped that these experiences would create new attitudes in the future practitioners and their families, and act as a recruiting device for the rural areas in the WAMI region.

The founders of the WAMI program felt that community clinical units could also serve as a focus for the continuing education of physicians in the area. In part, this was to be achieved by having inquisitive students interact with physicians over a period of time. In addition, the visits of the community-based faculty to the medical center and visits of the medical center faculty to the communities, would provide a continuing emphasis on learning. Finally, specific programs from the medical center could be transported to the community for use by all physicians in the area. In this way, the continuum of learning throughout professional life could be emphasized. Physicians in training could participate in the development and implementation of new policies and programs which may eventually affect them. In addition, consultation would be available to the communities and the sense of isolation that many rural practitioners feel could be reduced.

In addition to the community clinical units, the state universities without medical schools could play a major role in the process of continuing education for health professionals. This goal would be accomplished by periodic visits to the universities by faculty from the University of Washington School of Medicine.

Finally, it was hoped that the community clinical units could eventually be used to train the various health care professionals as a team. This development could lead to a more effective integration of their efforts and an awareness of the roles that each professional may play.

Rationale for WAMI Program

Considering the needs for health care in the WAMI territory, a number of justifications emerged for implementing the WAMI experiment.

- Provided the university phase of the WAMI program proves to be an effective way to teach the beginning portion of medical education, the WAMI program offers a way to increase the number of physicians in training without requiring new investments in "bricks and mortar." In addition, the WAMI program can reduce the impact that larger numbers of students would have on the medical center in Seattle.
- Since physicians, in large part, tend to practice in those areas where they received their train-

ing, the decentralization of a portion of the undergraduate clerkships and the residency training programs may reduce the maldistribution of physicians that now exists in the WAMI territory.

• It is now generally accepted that the AMI states, or those without medical schools, cannot financially support a medical school, nor are they paying the costs of educating their own residents in medicine. In addition, there appears to be no possibility of developing a single medical school which would serve more than one state in this area, as was proposed by Dr. Ward Darley in 1958 for Montana, Wyoming, Nevada and Idaho. WAMI provides an alternative solution to this dilemma by allowing a portion of educational appropriations of a given state to be spent in that state. Finally, WAMI offers the universities involved an opportunity to broaden their curricular offerings. These components of the WAMI program provide a basis for a partnership and, in turn, justify the expenditure of "state" funds at UWSM to pay the actual costs of medical education. As such, it broadens the base of support for medical education in the WAMI region and distributes the burden in an equitable way.

• If the WAMI experiment is educationally sound and financially and logistically feasible, then it will be possible to increase the opportunities for medical training available for students from all of the WAMI states, including the state of Washington.

• Through the efforts of the federal government and the medical schools, large numbers of highly trained basic scientists have been educated in the last 10 to 15 years. Some of these scientists are working as faculty members in universities without medical schools and were judged to be effective instructors during their graduate or postgraduate training. In addition, clinical training programs have produced a pool of highly trained manpower which may also be used for instruction. Such teaching represents a resumption of teaching activities required of residents or fellows. The WAMI concept provides a way to involve both manpower pools in the training of physicians without requiring that they be in Seattle.

• It was reasonable to assume that the community experiences will be of acceptable academic quality for a number of reasons. (1) The peripheral faculty are thoroughly evaluated before they are chosen to participate in the program. (2) The periodic visits by full-time faculty to the units and by the clinical (part-time) faculty to the medical center provide a continual monitoring of the program. (3) The educational experiences will, for most of the disciplines, occur after the students have received their basic hospital training in that discipline at the medical school. As such, the students will require less supervision in the community setting than they would require if this were their first major exposure to clinical medicine. (4) Since residents in the various disciplines are assigned to the units, they assist in the instruction of the undergraduate students in the same way they do in the medical center. (5) Learning resources support is being developed to amplify and reinforce the concepts and knowledge which are germane to the various curricular objectives.

• By decentralizing a portion of the clinical training for medical students and residents, the pressure on the clinical teaching resources at the medical center and affiliated hospitals is reduced. Access to patients in the communities will also provide students experience with diseases which they may not now see in university-related hospitals in Seattle.

• A decentralized program of medical education should provide a more effective basis for recruiting students, including disadvantaged students, from the WAMI area. For example, Alaskan native leaders feel the presence of the WAMI program will be instrumental in convincing native students that medicine is a career option for them. This is especially critical since only one Alaskan native is documented as having been admitted to a medical school.

• The decentralization of a portion of medical education has expanded the number and kinds of educational experiences available to medical students from the University of Washington. By capitalizing on the assets available inside as well as outside the metropolitan setting, students should have a broader background of knowledge, skills and understanding to apply in their professional lives. This background will also provide a better basis for selecting careers, and where these careers will be pursued, than has been available before.

• Should the WAMI concept of decentralized, cooperative medical education prove to be viable, then the concept may be transferred to other fields of health professional education. As such, it was expected that the presence of a medical education program in a state would serve as a central point around which a wide range of health-related education programs would develop.

• Because the WAMI concept envisioned using the University of Washington School of Medicine as a home base and incorporating facility and faculty resources already in existence elsewhere in the region, it was possible to implement WAMI more rapidly than most new medical education programs. The initial goal was to have the program in operation by 1971, or two years after birth of the plan. In fact, this was achieved in 15 months.

• If even a portion of these expectations for WAMI are realized, it is reasonable to conclude that the overall health of the people in the WAMI territory should be improved. This conclusion rests on the assumption that medical education as presently constituted, is ultimately beneficial to the health of people who make it possible.

Progress to Date

University Phase

In September 1971, nine students began the first semester of medical education at the University of Alaska. This experience was repeated in 1972 with 30 students in Alaska and Idaho and at the Washington State University. In 1973 Montana State University, the fourth and final university in the program, was added and 40 students, distributed equally among the four sites, were involved. It is anticipated that the entire first year of the curriculum will be provided at the University of Alaska beginning in the fall of 1974 and a similar program at the other universities in 1975.

While in these settings, the students enroll in courses which are equivalent to the courses being taught at the University of Washington Medical School. These courses are conjointly designed by the faculties of all universities involved, including UWSM. In addition, faculty from the University of Washington participate in the teaching program in the four institutions as visiting faculty. These visits and a conjointly designed evaluation of the program including a common examination at the end of each course are being used, along with National Board results and performance in subsequent courses, to assess the quality of education and to compare the performance of WAMI students with students who begin medical education in Seattle.

During the course "Medicine, Health and Society" the students visit rural villages in Alaska, Indian reservations in Idaho and Montana, migrant farm camps in Washington, and community clinical units in all of the states. These visits are designed to expose students to the problems in the delivery of adequate health care to rural areas of the WAMI region. The students also spend half a day per week working with physicians in the local communities to obtain an understanding of the practice of medicine in that community. The majority of these preceptors are primary care physicians.

Community Phase

The first two community clinical units were established in family medicine in Omak and Grandview, Washington, in March 1971. The selection procedure, which is used in establishing all units, involves informing the members of the State Academy of Family Physicians of the educational program available. Along with this announcement is a description of the objectives and a proposal which physicians can complete and return if they are interested. A joint selection committee composed of faculty from UWMS and practicing physicians then reviews the proposals and recommends sites to the Dean.

Since 1971, additional units in family medicine have been established in Oak Harbor and Anacortes, Washington, and in Kodiak, Alaska. In each of the units, two students are now spending six weeks under the supervision of physicians who have been given "clinical" (part-time) appointments in the Department of Family Medicine. Each unit is visited by "home-based" medical school faculty at least once every six weeks. In addition, the community faculty members come to Seattle two to four times a year for orientation, education and planning, and are paid for their educational effort under a contract with the University of Washington.

In addition to the family medicine units, a unit for obstetrics and gynecology has been established in the Treasure Valley of Idaho and involves the cities of Boise, Caldwell and Nampa. Three additional units in pediatrics are operating in Great Falls, Montana; Pocatello, Idaho and Spokane, Washington. Most recently, units have been established in psychiatry (Anchorage, Alaska) and in internal medicine (Wenatchee, Washington and Missoula and Billings, Montana). The 13 units will accommodate over 240 students and residents per year. This is equivalent to space for 26 full-time students and 13 full-time residents.

Principles Learned from WAMI Experience

University Phase

• A knowledgeable "coordinator" with financial and curricular authority is required at each peripheral university. This person must have an administrative supervisor in the university, but must also relate closely to the Director of WAMI, who is at UWMS.

• The conjoint admissions committee concept of having representatives from the admissions committee at the University of Washington and from each of the AMI states select residents from the AMI states for admission to medical school is a feasible way to have input from the participating states. Under the present accrediting regulations, it is necessary for the University of Washington to retain final responsibility for these decisions. Visits by the admissions committee members to the AMI states and to UWMS are required if the participants are going to fully understand each other.

• At least eight students are required for there to be a "critical mass" in each university program. While other students may enroll in the WAMI courses, the WAMI students must develop group cohesiveness, esprit de corps and a sense of professionalism if they are to have the appropriate learning experiences. Students have not felt isolated under these conditions.

• A quarter or a semester is the maximum educational period that a university without experience in medical education should undertake during the *first* and probably the second years of the experiment. Numerous unexpected problems preclude further curricular undertaking if the appropriately controlled experiment is conducted.

• While some existing courses will suffice for the WAMI curriculum, new courses must, in most cases, be developed. The extent to which new courses are required depends in large part on the faculty and curricular resources already in existence. When existing courses are used, special sessions to provide a medical orientation for the subject matter must be provided. This can be accomplished with films, tapes or visiting faculty from UWMS. While the equivalent basic experiences will be provided at each of the universities, it is recognized that each will also offer a unique experience.

• An extensive continuing evaluation program is necessary if questions about the "quality of the experience" are to be answered.

• Performance on examinations taken in common by students who have participated in the university phase of the WAMI program has been indistinguishable from that of students who have not been involved. Similarly, no distinguishable differences have been observed in WAMI and non-WAMI students in courses taken together in Seattle, on the National Board's "Minitest" or on Part I of the National Boards. A small number of the WAMI students have experienced academic difficulty, but the number and severity of these problems has not been greater than in the non-WAMI group. A higher percentage of WAMI students (62 percent), however, are choosing family medicine than are non-WAMI students (47 percent). This observation suggests that the WAMI program has an impact on the attitudes and career goals of the students.

• Students are satisfied with the decentralized approach and will recommend the program to their peers. Of the 78 students who have participated in the university phase, 93.6 percent say they would repeat the experience and the great majority (85 percent) say they would spend an entire year in WAMI if it were offered.

Community Phase

• There have been 159 students and 16 residents who have participated in the community phase. In addition, of the students who began medical school in the university phase of the WAMI program and who are eligible to participate in the community phase, 55 percent have chosen one community experience and 34 percent have chosen two or more.

• Of the first 97 students who spent a six-week clerkship in a family medicine CCU, 79 (82 percent) are still pursuing careers in primary care. Of these, 62 (64 percent) are in family medicine.

• Of the 16 students elected to Alpha Omega Alpha (AOA) and graduating in 1973, 10 had chosen family medicine and were admitted to family medicine residency programs.

• Fewer than 10 percent of the practicing physicians are able or willing to undertake a significant commitment to medical education in addition to an active practice. In addition, fewer than 5 percent of all physicians will devote the time required to become first class instructors. Hence, the presence of a resident in the community clinical unit has helped to provide a satisfactory education environment for students and the community faculty. The presence of the resident, however, has not

compromised in the minds of the student, resident or faculty the experiences available to the students in this setting by the "layering effect" seen in a university hospital setting.

• The periodic visits of faculty from the University of Washington to the community clinical units and vice versa have begun to open major opportunities for the continued education of health professionals. Rounds, special consultant clinics, lectures and discussions with medical personnel have all been initiated on the visits to the units. Both the physicians in practice and the visiting faculty wish to expand this opportunity further, as well as incorporate medical audit, such as Patient Care Appraisal, into the system. The participation of the community faculty in these programs is absolutely essential if students are to observe and, it is hoped, emulate these "role models" who continue to learn throughout professional life.

General

• Because of the limited learning resources support available in the region, the University of Washington must act as a resource to service the needs of all of the WAMI experiment. This is especially critical as the university phase of the program expands and as more of the educational process occurs away from the medical center. It is abundantly clear, however, that while tapes, films and programmed instruction materials are valuable for teaching, they will not replace the need for qualified faculty.

• With the exception of the Alaskan Health Sciences Library in Anchorage, only limited medical library resources exist in the WAMI territory. Consequently, students in all states have made significant use of the Pacific Northwest Regional Health Sciences Library which is located in the Health Sciences Center at the University of Washington. It is necessary, therefore, to develop library resources at each of the university and community sites.

• If the program is to have a long-term survival, financial support from the states involved must be obtained. In addition, the program must become an administrative unit within each of the cooperating universities. Such an administrative unit must have its own curriculum, faculty, space and budget authority.

• Among the major needs of the WAMI program, communication between the participants is of paramount importance. To meet this need, meetings, conferences, telephone conversations, reports, a newsletter and personal visits have been used. In the future, discussions and meetings will be conducted via the ATS-6 satellite launched by the National Aeronautics and Space Administration on May 30, 1974. This satellite allows for full duplex audio exchange (telephone-like conversations). In addition, two-way simultaneous color television image transmission (full duplex video) will be possible which opens multiple possibilities for communication that are not now available.

Difficulties Encountered

Of the problems encountered in an approach to medical education such as the WAMI program, the single most pressing political issue is the question, "What's in it for us?" Since the program crosses state lines, it deals with four state legislatures, four governors, four state medical societies and four university systems. In the case of Montana and Idaho, there are two or more institutions interested in being involved in the program. It is not surprising, therefore, to find on the subject of medical education differing views and dissimilar priorities among the groups involved. As a result, it has been imperative to define clearly what the benefits are for each party and why a cooperative approach is more beneficial than multiple independent efforts.

The overriding educational question has been about the quality of education that a WAMI student receives at a university without a medical school. The same question is repeatedly raised about the educational experiences in the community phase of WAMI. This issue, which is not completely settled, has been addressed by involving medical school faculty in planning, conducting and evaluating each area of the program. For example, the biochemist who is the chairman of the biochemistry course at the University of Washington School of Medicine, also chairs the planning session for courses which will be taught at the other four universities. He assists in reviewing potential faculty members, assists in the delivery of the course and directs the common examination given at each site at the conclusion of the instruction. Similarly, an academic internist in the Department of Internal Medicine designed, selected, initiated and monitors the community experiences in that discipline. In addition, personnel from the Office of Research in Medical Education (ORME) assist in the development of special or unique evaluation techniques and methods aimed

at answering special questions and concerns expressed by the faculty (such as National Board performances, performance of WAMI and non-WAMI students in courses at the University of Washington School of Medicine and performance on special examinations).

Another continuing challenge is the coordination of an effort that covers the distances and involves the number of people and institutions that the WAMI program does. The need for communication becomes critical at times and has required the use of newsletters, films and reports, as well as special visits and patience.

The Future

In the minds of many individuals the WAMI program holds great promise for the Pacific Northwest and Alaska. If this promise is to be realized, at least two developments must occur. First, the funding of the program must be assured through a continuing financial commitment by the states. While the AMI states have made a token commitment to the program for the financial year 1974, they will be required to assume the costs of educating their students if the program is to continue after June, 1975.

Second, the academic program must be accredited by the Liaison Committee on Medical Education of the American Medical Association and Association of American Medical Colleges. While no problem is expected in meeting the requirements of the Liaison Committee, a number of challenging issues remain to be settled.

In the future, it is possible that the WAMI concept will be adapted to other health science disciplines including dentistry, nursing, and selected allied health programs. Equally plausible is a regional network of residency training programs involving the medical center, selected community hospitals and various community based, office or ambulatory settings.

While the regionalization concept has been applied first to educational endeavors, it is appropriate to consider the possibility of further adapting the research and clinical resources of UWSM to serve regional needs. In the case of research, the existing Regional Primate and Regional Cancer Centers could develop programs for the entire region. In addition, planning for additional centers could be oriented toward meeting regional needs. In the case of clinical medicine, UWSM could become a regional resource providing consultation and tertiary care to the people of the WAMI territory. In programs such as this, modern communication technology including satellites may play a major role. Only time will tell whether this potential is realized.

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Quality of Care and Utilization Assessment

The Hospital Response to PSRO

WOODBURY PERKINS, MD, *San Diego*

GROWING PRESSURES from a variety of directions to determine the quality and cost of care delivered in hospitals have provoked almost uniform resentment. This response by physicians and hospital administrators stems from rules and regulations imposed by outside sources, especially by the federal or state governments. In addition, the current demands for quality assessment pose many basic issues for the medical staff concerning approaches to assessing quality of care and proper utilization of facilities which are different than traditional methods.

This article offers examples of medical staff quality assessment activity which have been locally designed and conducted voluntarily. Similar programming to document effective peer review can be effected in any hospital to preserve local independence by fulfilling PSRO requirements. The article is designed to assist the medical staff of any hospital by offering answers to some of the most commonly asked questions, such as:

- What is the matter with the traditional committee approach (use of the credentials committee, tissue committee, supervisory committee and the like) to assessing quality of hospital care?—"We have been doing this for years; why do we now have to do medical audit?"
- Which audit approach is best, the American Hospital Association's Quality Assurance Program (QAP), the Joint Commission on Accreditation's Trustees, Administrators and Physicians workshops (TAP), or the CMA-CHA Medical Audit Programs?
- Who is to define quality? How can one measure or tabulate the quality of anything (quality being a matter of subjective value judgment)? Is this "cookbook" medicine?
- What is the relationship between costs of care and quality?

Traditional Method and Newer Approaches

To answer the first question, there is nothing the matter with the existing hospital committee approach, and it must continue. The traditional hospital committees function as a peer review mechanism. Individual physician performance is examined. The credentials committee is essential for approving and reappointing individual members of the medical staff. The tissue committee is helpful in identifying errors and needless surgical operations. Supervisory committees are necessary for the development of departmental rules and regulations, and for maintaining departmental member discipline. These are essential functions to maintain. However, focusing on individual per-

Submitted, revised, June 21, 1974.

Reprint requests to: W. Perkins, MD, 4077 Fifth Avenue, San Diego, CA 92103.

formance may overlook deficiencies of institutional or group attitudes and performance. The purpose of medical audit is to focus on group performance by reviewing a disease or procedure topic. While focusing on group performance, some of the activities of many hospital committees can be merged, sparing time and effort of the medical staff. This has been demonstrated by Robinson.[1] The medical audit approach does not replace a one-on-one peer review method of assuring quality of hospital care; what it does do is augment and supplement the assurance by an evaluation of institutional performance. When local group or institutional needs for improving quality of care are identified, remedial action is initiated locally. In short, medical audit prevents losing sight of the forest for the trees.

Different Approaches to Audit

Concerning the different medical audit approaches proposed by QAP, TAP, CMA-CHA, and others,[2] to assessing the quality of patient care, there are only minor procedural differences. All are patterned after concepts developed by Clement Brown[3] which measure performance against pre-selected criteria linking identified needs to continuing education programming. Originally QAP was basically a process-oriented method; TAP focuses more on a screening mechanism of chart review with attention to outcomes; the CMA-CHA procedure includes elements of both process and outcome but, in addition, features an institutional commitment by broad participation and ratification by the staff.[4] Any of these methods are acceptable to the Joint Commission, to the CMA or to a PSRO as a program for quality assurance. An essential element of the audit approach, often overlooked by those expressing the most resentment, is the value of local medical staff review activity rather than adopting standards recommended from outside sources. Linked to the process of evaluating the quality of care rendered is an organized continuing education process designed to remedy identified deficiencies. In essence, the primary objective presumes that local assessment of quality of care and utilization of facilities will make unnecessary outside rules and regulations, and will assure the best for the patient.

What Is Quality and How Is It Measured

Defining quality is probably the most difficult phase for a hospital audit committee which is assigned the task of assessing quality of care. All physicians know what quality is, but the difficulty arises in trying to develop standards of institutional care which are realistic, attainable, and flexible in relation to the many variable factors inherent in the management of human beings with disease or illness. Another difficulty in establishing quality standards is the variation of individual physician experience and bias.[5] In order to develop appropriate standards of quality, the current method advocates the use of explicit criteria.

Explicit criteria are those which are maximally objective and designed by the group. In contrast, implicit criteria are those frequently used in traditional committee work based upon the individual reviewer's opinion, feelings and judgment concerning issues of quality or utilization while reviewing a single chart. Developing explicit criteria is hard work and time-consuming. Required is defining the purpose and scope of a disease or topic review and then developing objective standards of optimal care which are both realistic and measurable. For example, a Medical Audit Committee set about to determine the frequency of unrecognized hypertension among patients admitted to the hospital for another primary cause. First, the committee argued at length as to what constituted hypertension. Some said a diastolic pressure of 90 mm of mercury, others said a diastolic of 100 mm and so on. Someone raised the point that a patient 85 years old might be expected to have elevation of the diastolic pressure yet obviously not be in trouble with hypertension. Next, they argued about who was going to take the blood pressure. Was a nurse assistant's recording as valid as physician's recording? And, how often did the patient have to have recorded elevation of blood pressure for it to be considered significant? Then a problem arose as to what is "unrecognized" hypertension. Did that mean the doctor neglected to make specific mention of the blood pressure on the progress sheet, or that an antihypertensive medication was not ordered, or that specific laboratory studies directed at identifying the source of hypertension were not recorded?

These various issues, concerning the purpose of the review and a definition of expected optimal performance, were finally resolved after several meetings of the committee. The committee designed a review to look at two hundred sequential discharges from the medical and surgical services of patients between the ages of 20 and 60 without a primary or secondary diagnosis of hypertension.

To do this, they tabulated on a data-gathering worksheet any record of diastolic pressure of 100 mm of mercury or higher, recorded on two or more occasions by two or more observers. To settle the question of whether or not hypertension, by these criteria, was "unrecognized," the committee made up a short list of antihypertensive drugs and specific hypertension related laboratory studies which should be included on the chart or mentioned on the progress record, to indicate that hypertension was recognized. Having spelled out these details, the committee then reviewed quickly, with the aid of the record room, defined sequential discharges of patients from the medical and surgical services who had been admitted for unrelated medical or surgical reasons.

What the committee had done, before the review, was to take several important steps. It had stated the objectives of the study and had framed the scope of the study in realistic terms. The focus was on the recorded action or performance of a group to determine whether or not anything had been done about hypertension, and it had defined for performance evaluation a set of expected quality standards which were measurable. There was no emphasis on nor concern with individual physicians' performance.

The value of this approach is that when a group participates in establishing the definition of quality of care for themselves with their own hospital population, then they will act as a group in response to deficiencies detected and will take appropriate action without any outside pressure. When this is done locally, it avoids the "cookbook" approach to medical practice, and it also avoids computerized national norms or other published norms which, in effect, threaten individuality and independence. In addition, such local hospital activity is compatible with PSRO requirements and accordingly, helps alleviate the frustrations.

Cookbook Medicine and Local Values

Concerning "cookbooks" and computers, lists of criteria for quality performance in a variety of diseases are available from several sources. One such computerized design for assessing acute myocardial infarction is tempting, though of questionable value for its stated purpose. It contains 42 data elements to be extracted from the records for measuring the quality of care in this disease. Forty-one of the elements are process-oriented and only one, length of stay, is outcome-oriented. The process questions to be recorded largely revolve about elements of the patient's history and physical examination recorded on the chart, and elements of care rendered, such as frequency of blood pressure monitoring and whether or not fluid intake and output were measured. All of these are significant elements of data to be contained in the hospital record of a patient with acute myocardial infarction. However, despite all the data put forth on computer print-outs, the results give only passing relevance to the quality of care because no action-related values are associated with the elements of data extracted. Presumably, the patient received good care if all 41 of the process elements were recorded as "yes." But what if only 30 or 35 of the elements had been recorded "yes"? Did the patient get good care or didn't he? All data must be interpreted by a person and a value judgment attached. The computer cannot do that.

A more effective approach is to identify the relevant elements of data in relation to the objectives of the study and to establish a value judgment concerning the elements before recording the data. Information gathered concerns only those few selected measurable elements and is compared to the preset values. For example, as to acute myocardial infarction in the computerized program mentioned, the data would have much more meaning if a single outcomes element, say mortality rate, were determined. There are enough available data to set up a standard that the mortality rate for patients with acute myocardial infarction in the modern hospital should be between 15 and 20 percent. If a hospital reviews its own experience and finds the mortality rate for acute myocardial infarction to be 25 or 30 percent, then there is cause for it to review its own process of care to find an explanation. The outcomes element referred to—length of stay—is irrevelant to the quality of care, unless possibly it focuses on short stay practices.

Relating Costs of Care with Quality

What about proper utilization of the hospital facilities stressed in P.L. 92-603? This is a cost containment element, and the current yardstick is length of stay. Does length of stay really reflect proper utilization, and is this really an effective cost control mechanism in dollars saved? Since 1965, for purposes of reimbursement, hospitals have had utilization review committees which, in the main, have focused on reducing the length of

TABLE 1.—*Length of Stay Data*

	1970	1971	1972	1973
Total discharges (med-surg)	18,367	18,621	18,880	19,603
Total transfers to convalescent home (med-surg)	920	945	1,005	890
Average length of stay (in days) (med-surg)	7.5	7.0	7.2	7.1
Occupancy (med-surg) (percent)	87.04	85.57	84.99	83.52
Average daily room charge (med-surg) .	$59.79	$65.93	$70.63	$75.93

TABLE 2.—*Cerebral Vascular Diseases, Medical Service Annual Review H-ICDA No. 435 April Through September*

	1969	1970	1971	1972	1973
Total patients H-ICDA 430-438 ..	214	178	164	179	182
TIA, H-ICDA 435 .	6.54%	15%	22%	19%	28%

stay. Attention to pre-admission screening may become an additional task. From the point of view of the hospital administrator with an occupancy rate of 50 or 60 percent or lower, the per diem rate will have to go up as occupancy falls, or he will have to restrict services (and thus quality), or he has to generate operational funds from some other source. The United States is already overbedded, according to the AHA, and most of the metropolitan areas in California have an excess of beds today.

In one 500-bed acute care hospital, with an active and conscientious utilization review committee whose members laboriously pore over hundreds of charts every month with a focus on length of stay, Table 1 demonstrates what has happened in terms of medical-surgical adult patients over a four-year period.

There was a modest increase in the number of admissions as expressed by discharges. The number of patients transferred to convalescent homes was not significantly changed over the four-year period. The average length of stay dropped from 7.5 to 7.0 days between 1970 and 1971, but after 1971 remained essentially unchanged. In spite of the increased number of patients in the hospital, the occupancy percentage dropped slightly in each of these years (14 beds were added to the hospital facility in 1973). Despite the labors of the utilization review committee, the per diem room rate steadily rose because of multiple indirect economic factors with which everyone is familiar.

Linking utilization review with attention to quality of care can be a more relevant effort. One hospital, in an effort to assess the quality of care for a common admission to the medical service, decided through its audit committee to do a pattern-of-care review of the disease entity "stroke." Many hospitals pick this disease entity to review, as it is a frequent cause for admission. But stroke is a somewhat difficult disease to audit because the diagnosis is often vague and because the diagnostic nomenclature contains "wastebaskets." Specifically, there are nine subclassifications of cerebrovascular disease, H-ICDA 430 through 438. The audit committee discovered this problem early on and, accordingly, decided to limit its review to the transient cerebral ischemic attack (TIA), H-ICDA 435. Here, at least, was one cerebrovascular disorder about which possibly something could be done. In 1969, the committee set up its criteria for good management of the patient with TIA and began to measure what was going on. It has continued to measure the same diagnosis ever since, and Table 2 shows what has happened.

The number of patients distributed among the nine H-ICDA diagnostic categories for cerebrovascular disease during a consecutive six month period in 1969 was 214. Of this group, TIA was diagnosed in 6.54 percent. The committee was concerned with this low percentage of specific diagnosis and suspected that patients with this potentially correctable disorder might be misdiagnosed into one of the other vague categories, such as acute ill-defined cerebrovascular disease or general ischemic cerebrovascular disease. Educational programming was constructed relative to the signs and symptoms of TIA in an effort to develop more precision in the diagnosis of a potentially correctable defect.

Since 1969 there has been a fairly constant number of patients discharged from the medical service with a "stroke" category diagnosis. Important to note is that the hospital structure did not change during these years. There were the same facilities for angiography in 1969 as in 1973, and there was no new neurologist, neurosurgeon or vascular surgeon on the physician staff. The variables did not change. In addition to these medical discharges, the number of patients with the same diagnosis discharged from the surgical service (not shown on Table 2) increased, indicating more surgical therapy.

As the diagnosis was made more frequently, the number of angiograms, brain scans, and neck

operations increased. The hospital facilities were much better utilized in 1973 in this regard than they were in 1969, but the cost of medical care rose because of the increased number of procedures. However, the quality of care was presumably better for this disease in 1973 than it was in 1969. To document quality rather than cost containment reduces frustration over threatened regulations.

On the other hand, costs need not always go up. Linking utilization and quality of care with resulting reduction of costs yet improvement in quality of care, was demonstrated by a pediatric audit committee looking at the use of mist tents in children. In 1971 there were 167 children discharged with a diagnosis of respiratory tract disease which included pneumonia, bronchitis, asthma and upper respiratory tract infection. Sixty-seven of these children, or 40 percent, were placed in a mist tent for an average of two days per patient. The pediatric audit committee developed criteria for proper use of a mist tent and then set about to find out what they were doing in relation to their criteria. What they found out about themselves was disturbing. For example, of the 67 children, 33 had oxygen piped into the tent without an order by the physician. Someone had plugged the intake tube into the wall oxygen socket rather than the room air socket. This explained why the majority of children were cold and had recorded rectal temperatures below 98°F. In comparing their actual performance with their criteria for use of a tent, they found that only 36 patient days out of 134 patient days were clinically justified. This fact was further disturbing because the average charge per patient for the tent was $66.80. Simply by taking a look at what they were doing in relation to their own optimal care criteria, the pediatric department voluntarily reduced the indiscriminate and inappropriate use of mist tents. Consequently, there was better utilization of equipment, patient charges were saved and the quality of care was improved.

The experience cited demonstrates the value of more appropriate attention to utilization than a superficial cost-saving, length-of-stay focus.

Patterns of Care Review; Medical Audit; Continuing Education

A pattern-of-care review differs from medical audit in that it gives an overview of activity without specific orientation to quality. A pattern-of-care review may reveal a gross deficiency such as a high mortality rate, or the use of antibiotics inconsistent with sensitivity studies. Such findings indicate a need for a detailed examination of the problem to identify the reasons for the deficiency. Results of a pattern-of-care review are frequently interesting to the staff, but in general do not contain a call for remedial action.

Medical audit, on the other hand, is the process of measuring existing performance against present criteria for excellence, utilizing a level of acceptable performance as an indicator of the need for corrective action.

A pattern-of-care review can be likened to taking a test in mathematics ranging from simple arithmetic to calculus, in which the answer to each question is marked *right* or *wrong* but no passing grade for the test is established. Implicitly, the person taking the test will know what he got right or what he got wrong when the test is scored. Medical audit, on the other hand, limits the scope of the test, announces ahead of time what the passing grade will be, and designs appropriate remedial action if the test is "flunked."

A pattern-of-care review is often a helpful way to develop medical audit in order to identify deficiencies in quality of patient care. For example, a medical department audit committee conducted a pattern-of-care review in 1970 for acute myocardial infarction in order to develop a data base for future audit. In a review of 251 patients with a confirmed discharge diagnosis during a nine-month period in 1970, two items of information caught the attention of the committee. First, 70 percent of the patients were monitored and 30 percent were not. Second, the death rates for those monitored and those not monitored appeared to be essentially the same—21.4 percent for the monitored group and 24.3 percent for the group not monitored. The staff felt that the mortality rates were too high, and in addition some members felt the results indicated the monitoring unit was inefficient and useless because of the similarity of death rates between the two groups. Others argued that only the sicker patients were monitored. The information pointed up the fact that no one really knew what was going on. It was decided to do a more detailed review of all deaths with focus on the day of death, where in the hospital the death occurred, and the physiologic cause of death. This revealed that half of the patients in the monitored group died after discharge from the monitored unit while receiving general floor care.

TABLE 3.—*Acute Myocardial Infarction, January Through September*

	1970	1972
Total number of patients	251	214
Under 66 years of age	48%	48.3%
Males	60%	59%
Length of stay (survivors)	(days) 16.7	(days) 17.8
Percent patients monitored	70%	87%
Percent patients non-monitored	30%	13%
Survivors	195	183
Deaths	56=22.30%	31=14.40%
Death rate of non-monitored	18=24.32%	6=21.43%
Death rate of monitored	38=21.40%	25=13.44%
Death after discharge from monitoring	17 of 38=44.70%	3 of 25=12%

TABLE 4.—*1974 Criteria for Acute Myocardial Infarction*

	Expected Compliance (percent)
Diagnostic accuracy	
At least two	
Classical EKG changes	100
Specific enzymes rise	
Classical clinical history	
Monitoring unit	85-90
Mortality rates	
a. All patients, all ages, not to exceed	20
b. Monitored patients, age 75 & under	<15
c. Non-monitored patients, age 75 & under	20
d. Preventable cause of death	< 5

Some of these deaths were expected, but seven of the 38 deaths were sudden and unexpected. These deaths were reviewed by a panel of cardiologists and considered to be due to late arrhythmia (autopsy was done in five of the seven cases). This evaluation posed serious question as to whether these patients had been discharged from monitoring too early. Another possibility was inadequate attention to the patient on general floor care. Detailed review suggested the latter. The data were reported by the medical audit committee to the medical supervisory committee with recommendation that when a patient was discharged from a monitored unit to general floor care his chart should be clearly flagged. Accordingly, a sticker was devised, *previously monitored* in red, which was placed on each chart and on the card index at the nurses' station. Other recommendations made by the audit committee to the medical supervisory committee were that closer to 90 percent of patients with acute myocardial infarction should be monitored in the hope of reducing the mortality rate, and that in-service educational programming be structured for general floor care personnel.

A repeat performance review was then conducted for the same time span in 1972. Table 3 shows a comparison of results. Data on age group, sex and length of stay were essentially the same in 1972 as in the 1970 study. However, the mortality rate for all patients, irrespective of age, had dropped from 22.3 percent to 14.4 percent. The proportion of patients monitored had risen from 70 percent in 1970 to 87 percent in 1972. And the death rate for patients who were monitored had dropped from 21 percent to 13 percent. Finally, the number of late deaths of previously monitored patients had dropped to three, only one of which, on review by the cardiologists, was considered preventable (late arrhythmia); the other two patients were in their late 80's and had had protracted congestive heart failure.

These data suggest an improved quality of patient care brought about through locally designed and conducted patient care review with corrective action directed at identified institutional needs. Furthermore, remedial action was conducted by educational techniques which resulted in procedural changes without threatening any physician, revealing any identities, or taking any punitive action.

The same group has now designed its review program for 1974. Having a data base established in the review of 1970 and 1972 now permits an outcomes-oriented set of criteria for good care in cases of acute myocardial infarction, as shown in Table 4. The only element in the process of care being recorded is whether or not the patient is monitored. The significant element in the measurement of quality of care will be an outcomes element, mortality rate. Presumably, if the mortality rates match the 1972 statistics, or are even better, then the process of care must be acceptable. This simplified set of outcome-oriented criteria, with expected compliance figures, stands in contrast to the previously mentioned computerized program for measuring quality of care for the same disease with 41 process elements plus

one outcome element, length of stay—data which when pooled has questionable relationship to a quality judgment.

Conclusions

It seems certain that programming to assess quality of care in conjunction with assessing appropriate utilization of hospital facility is a current trend which will continue for several years in response to pressures from a variety of sources.

While the traditional mechanisms for peer review of individual performance are still essential, they should be augmented by the medical audit approach for determining group or institutional performance. Answers have been offered to commonly asked questions about methods of determining quality of care in the hospital setting.

When individual peer review and medical audit are implemented in a single hospital, utilizing locally developed standards for quality of care, an effective alternative is provided to externally imposed regulations.

By developing relevant, explicit criteria and defining the details of a review, any medical staff can conduct patient care assessment and assure quality of care by continuing educational programming.

Elements of appropriate utilization of hospital facilities, in addition to length of stay review, can be incorporated into a medical audit program in quality of care assessment.

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Notes from Important or Unusual Meetings

International Health

Report of the 27th World Health Assembly of the World Health Organization, Geneva, Switzerland May 7-24, 1974

FRANCIS W. PARNELL, MD
San Rafael, California

THE 27TH WORLD HEALTH ASSEMBLY of the World Health Organization was held in Geneva, Switzerland, May 7-24, 1974. Members of the United States delegation are as follows:

Chief Delegate:

Charles C. Edwards, MD, Assistant Secretary for Health, Department of Health, Education and Welfare.

Delegates:

Francis L. Dale, Ambassador, United States Representative to the European Office of the United Nations, Geneva.

S. Paul Ehrlich, Jr., MD, Director, Office of International Health, Department of Health, Education and Welfare.

Alternate Delegates:

Milo D. Leavitt, MD, Director, Fogarty International Center, National Institutes of Health, Department of Health, Education and Welfare.

Francis W. Parnell, MD, of San Rafael, a Clinical Instructor, Department of Otolaryngology, University of California, San Francisco.

David J. Sencer, MD, Director, Center for Disease Control, Department of Health, Education and Welfare, Atlanta, Georgia.

The World Health Organization (WHO) is composed of the World Health Assembly, the Executive Board and the Secretariat. The World Health Assembly, composed of 140 member nations, meets in regular annual sessions and determines the policy of the World Health Organization. In addition, it appoints and reviews the reports of the Director General and approves the annual program and budget.

The purpose and intent of the various United States position papers was to provide comment on the various agenda items felt to be most important, and to provide constructive criticism and helpful direction to the Director General and the Secretariat of the WHO.

The most significant items of medical interest that came before the World Health Assembly included biomedical research, the long-term planning of international cooperation in cancer research, human health and the environment, immunization, and the various WHO programs including onchocerciasis (river blindness).

A significant portion of the United States position paper on biomedical research was devoted to the "brain-drain" problem, since qualified health researchers often seek other opportunities for productive employment of their skills especially in the developed countries. Also, attention was directed to the possible role of WHO in the evaluation of the use of human subjects for clinical experimentation. The United States co-sponsored a resolution reaffirming the importance of biomedical research in solving practical health problems of the economically developed and developing countries alike.

Another of the major items on the agenda was the long-term planning of international cooperation in cancer research. The Director General was requested to continue the work that has been started by WHO on a comprehensive program for international cooperation in cancer research and methods. The role of the International Agency for Research on Cancer in Lyon, France, was stressed in the United States position paper. The International Agency for Research on Cancer is the principal global agency for the coordination and implementation of cancer research in the fields of epidemiology, environmental carcinogenesis and related activities.

The United States co-sponsored a resolution drawing attention to dangers of biological pollution of the environment caused by lack of basic sanitary measures, particularly adequate water supply and waste disposal facilities. The resolution urged member states to make immediate and

Reprint requests to: F. W. Parnell, MD, 750 Las Gallinas Avenue, Suite 205, San Rafael, CA 94903.

long-term protection and promotion of human health the basis for their environmental policies.

Immunization campaigns were stressed in another United States co-sponsored resolution on the WHO expanded program on immunization. The Director General was requested to intensify activities pertaining to the development of immunization programs especially for the developing countries, as well as to continue support of research on the efficacy of vaccines. It is noted that in extensive regions of the world, immunization is still available for only a small portion of the children in the susceptible age groups.

The discussion of the onchocerciasis (river blindness) program was most interesting since it is estimated that among the 10 million inhabitants of the area of the Volta River basin in Africa, more than one million are infected with onchocerciasis and, of that million, at least 70,000 are considered economically blind and many more suffer visual impairment. This disease, carried by the black fly, constitutes the most important deterent to human settlement and development of the fertile valleys of the Volta River basin which are now essentially uninhabited and nonproductive. Since there is still no drug suitable for mass chemotherapy, a massive multilateral aid program has been instituted and is scheduled to begin in November 1974. This is a 20-year effort to eliminate river blindness, and a resolution was adopted urging the countries that provide bilateral and multilateral aid through special health programs to consult with WHO for best coordination of effort.

It is necessary to stress the great relevance of the role of WHO to the practicing physician as it affects him in daily practice due to the increasing mobility of the patient population in the jet age. There are many examples of this relevance, including immunization, the possible global eradication of various diseases, especially smallpox, the epidemiologic aspects of cancer, and the global aspects of venereal disease.

Refer to: McMillan DE, Amacher P: Conference on the pathophysiology of diabetes mellitus (Notes from Important or Unusual Meetings). West J Med 121:350-355, Oct 1974

Notes from Important or Unusual Meetings

Conference on the Pathophysiology of Diabetes Mellitus

DONALD E. McMILLAN, MD
Santa Barbara, California

PETER AMACHER, PH D
Santa Ynez, California

A WESTERN REGIONAL CONFERENCE on diabetes mellitus was held at The Kroc Foundation in the Santa Ynez Valley of California, November 13-16, 1973. The purpose of the conference was to bring together some of the persons active in diabetes research in the western United States. Twenty-four investigators attended the conference and discussed papers given by 13 of them. In addition two brief presentations were made. This report summarizes the 15 presentations for those interested in current western diabetes research activities.

The first was by Peter H. Bennett, MD, acting chief of the Southwestern Field Studies Section, National Institute of Arthritis and Metabolic Diseases, Phoenix, Arizona. He brought up to date the information about continuing work on diabetes in Pima Indians. The Pimas have the highest prevalence of diabetes of any population in the world. Essentially half of all Pimas beyond middle age have diabetes as measured by glucose intolerance. Extensive observations have been made on the Pimas for this reason, and Dr. Bennett described the relation between serum insulin and glucose levels after a glucose load. The immunore-

Dr. McMillan is Director of Diabetes Research, Sansum Medical Research Foundation and Co-Chairman, Western Regional Conference on Diabetes; Dr. Amacher is Assistant to the President, The Kroc Foundation, Santa Ynez, California.

Reprint requests to: D. E. McMillan, MD, Sansum Medical Research Foundation, Post Office Drawer LL, Santa Barbara, CA 93102.

active insulin (IRI) level two hours after a glucose load was analyzed. Between glucose levels of 80 and 160 mg per deciliter the IRI rose as glucose rose, but above 160 mg per deciliter of glucose it fell as glucose increased. The same biphasic relationship between IRI and glucose has been observed in a study by Eschwege on Paris policemen. Although obesity increases IRI at all two-hour glucose levels, it has no effect on the position of the IRI maximum at 160 mg per deciliter glucose. Dr. Bennett next examined long-term studies of insulin response to ascertain whether specific IRI response patterns preceded glucose tolerance. Deteriorating glucose tolerance was preceded by higher two-hour IRI levels, but both phenomena were seen more in overweight Pimas. Obesity complicated the analysis, for it was associated with both future deterioration of glucose tolerance and higher two-hour serum insulin level. When deteriorating glucose tolerance of non-obese persons was compared with stable glucose tolerance of non-obese persons, no IRI response difference could be demonstrated. Dr. Bennett concluded that no abnormality of insulin production could be demonstrated to be present before diabetes develops.

Maurice E. Krahl, PhD, professor and chairman, Department of Physiology of Stanford University School of Medicine, briefly described his observations on fragmented growth hormone. He has been examining the possibility that a product of growth hormone might inhibit glucose utilization and hence be responsible for the hyperglycemia seen several hours after growth hormone administration. A fragment obtained from human and sheep growth hormones of less than 1,800 daltons molecular weight produced hyperglycemia in the ob/ob mouse. The fragment itself is probably from the C-terminal area of the intact growth hormone molecule.

Mayer B. Davidson, MD, assistant professor of medicine of University of California, Los Angeles, School of Medicine, described his studies of the effect of insulin and glucagon on glucose metabolism in rat liver. Using liver slices in a high potassium buffer, he demonstrated that insulin has several effects. It increases glycogen generation from either glucose or glycerol, in the medium, and accelerates lipid synthesis from glycerol. It inhibits gluconeogenesis from increased alanine, glycerol, or fructose. Insulin produces a simultaneous decline in glucose release and an increase in glycogen production; the conversion of radioactive glycose to carbon dioxide is unaffected. Glucagon effects were studied using liver slices in a low potassium buffer. Glucagon did not counteract the inhibition of gluconeogenesis produced by insulin. On being informed that glucagon content was monitored by radioimmunoassay, Dr. Unger stated that it was questionable whether glucagon detected by immunoassay in an *in vitro* study was still biologically active. After the conference Dr. Davidson confirmed the biologic activity of glucagon in his system by demonstrating that glucagon did produce glycogenolysis in liver slices from fed rather than fasted rats. He concluded that glucagon does not compete with the direct inhibition of gluconeogenesis by insulin.

Daniel Porte, Jr., MD, professor of medicine and chief of the Endocrinology Section, University of Washington School of Medicine, presented studies of neural influences on insulin secretion. He demonstrated the role of the sympathetic nervous system, first showing that the beta adrenergic agent, isoproterenol, can stimulate early insulin release even in patients who do not respond to glucose. Propranolol, the beta adrenergic blocker, stopped isoproterenol-induced insulin rise, but had no effect on glucose-mediated insulin elevation. He reported a patient with grossly abnormal carbohydrate tolerance whose plasma insulin initially fell rather than rose when glucose was given. Infusion of the alpha adrenergic blocker, phentolamine, resulted in improved glucose tolerance and a restoration of the early phase of insulin release. He then discussed the role of the central nervous system in insulin secretion. Rats given injections of insulin or tolbutamide became hypoglycemic. If the injections are repeated several days in a row, the animals will become hypoglycemic even if saline solution rather than insulin is injected. This conditioned response apparently involves both the pancreas and vagus nerve since it is abolished by streptozotocin or vagotomy. Atropine also abolishes the hypoglycemia, suggesting that the parasympathetic nervous system is involved. A central mechanism modifying insulin production was suggested by additional studies. Pancreatic insulin release and hypoglycemia were produced by injection of normal but not denatured insulin into the cerebral spinal fluid. Vagotomy blocked the response. Dr. Porte proposed that these observations could be explained by a central nervous system area which responds to changes in glucose metabolism by causing insulin release.

R. Philip Eaton, MD, associate professor of medicine, University of New Mexico School of Medicine, discussed glucagon and insulin secretion in glucose-fed rats and cobalt-treated rats. Animals fed 60 percent glucose in saline solution as their total diet for one week were found to have improved glucose tolerance even though blood insulin levels were lower. In the liver of glucose-fed rats, levels of several metabolic intermediates were found to have a pattern like that produced by high insulin levels in other circumstances. Dr. Eaton concluded that this similarity was due to increased liver sensitivity to insulin. This concept was supported by his observations of phosphoenolpyruvate carboxykinase levels in these animals. The glucose-fed rat retained a normal hyperglycemic response to administered glucagon, but it had a low endogenous blood glucagon level. Arginine administration produced glucose, insulin and glucagon responses below those of controls. Experiments carried out in colbalt-treated rats were then described. Glucose tolerance remained similar to that in controls but insulin levels decreased, free fatty acids rose, and liver phosphoenolpyruvate fell. Glucagon administration did not produce a normal blood glucose rise and did not cause insulin release, but its injection did change the levels of glucose intermediates in the liver and increased the rate of glycogenolysis. In cobalt-fed rats, arginine produced greater hormone responses than in the controls. Dr. Eaton speculated that diet or hormonal agents may change liver sensitivity to insulin through effects on the activity of gluconeogenic enzymes.

Roger H. Unger, MD, professor of internal medicine of the Texas Southwestern Medical School and the Dallas Veterans Administration Hospital, proposed glucagon and insulin as major factors controlling pathways of metabolism in the face of a varying dietary pattern. Glucagon opposes the action of insulin, for it is produced when no food is ingested, while insulin is produced when food is consumed. Levels of the two hormones vary in a reciprocal manner effectively represented by the insulin-glucagon ratio. The ratio may rise to as high as 70 to 1 after a high carbohydrate meal, but in starvation it falls to below 1 to 1. Glucagon levels have also been observed to increase when plasma volume falls. Ketoacidotic diabetic patients have very high glucagon levels, in part triggered by the decline in plasma volume in this condition. The high glucagon levels probably produce the increased numbers of hepatic lysosomes seen in ketoacidosis. Diabetic patients, even under good control, have increased fasting glucagon levels, poor suppression of glucagon by hyperglycemia, and excessive glucagon response to amino acids. Negative nitrogen balance develops in insulin controlled diabetic dogs and they produce large amounts of urea when given small amounts of glucagon. In conclusion, Dr. Unger speculated that lowering glucagon levels by pharmacologic means such as somatostatin might be beneficial to diabetics. In discussion, Dr. Rachmiel Levine pointed out that neither glucagon nor insulin is absolutely required for metabolic alteration; he cited the Houssay animal as evidence. Dr. Unger indicated that some enteroglucagon might be produced by Houssay animals, for it is found in pancreatectomized humans. He recalled human cases where no glucagon was measurable and agreed with Dr. Levine that the two hormones are tonal in character and not absolutely necessary. He asserted that insulin and glucagon are essential for metabolic flexibility in a changing environment.

Paul M. Beigelman, MD, associate professor of medicine and pharmacology, University of Southern California School of Medicine, reported on the release of insulin from isolated single islets. He reviewed the morphologic aspects of insulin release demonstrated by electron microscopy. Islets stimulated by high glucose levels develop increased rough endoplasmic reticulum, fusion of cytoplasmic vacuoles, and hypertrophy of the Golgi apparatus. He studied the release of insulin in a zero glucose medium and found that healthy islets released less than 15 microunits of insulin in a 15 minute period. A small amount of insulin was regularly detectable suggesting low level insulin secretion in the absence of glucose. Glucose stimulation resulted in more than a doubling of insulin production in almost all islets studied. A new technique was developed to measure insulin production by single islets. A "dip-stick" pipette was used to immerse one islet for 15 seconds into each of a series of wells on a rotating table. Results were preliminary, but suggested that insulin secretion is pulsatile in character, with an average oscillation period of 60 seconds in glucose-free medium and 42 seconds in 300 mg per deciliter of glucose. Oscillation might be an important factor in insulin secretion, each islet functioning as a physiological syncytium.

Karl E. Sussman, MD, associate professor of medicine of the University of Colorado Medical

Center, and chief of the Medical Service of the Denver Veterans Administration Hospital, described his studies on the association of adenine nucleotides and insulin release. In the adrenal medulla it is known that exocytosis of hormone-bearing chromaffin granules is associated with adenosine triphosphate (ATP) release. Dr. Sussman used isolated rat islets in perifusion studies and was able to demonstrate an abrupt rise in ATP in the medium when insulin was released following a 300 mg per deciliter of glucose challenge. The rise in ATP and the amount of insulin released were correlated. Radioactive percursors of ATP were used to determine whether the release of ATP and insulin occurred simultaneously. Radioactive ATP was released with insulin from glucose-stimulated islets when incubation with radioactive adenine had been prolonged sufficiently to label the insulin granules. An effort was also made to identify the source of the released ATP. Using sodium fluoride and Antimycin A, Dr. Sussman showed that insulin release could be blocked without total depletion of islet ATP. He concluded that two ATP pools were present in beta cells. Mitochondrial ATP apparently supplies energy for insulin release to the other pool in the beta granules which then is unaffected by mitochondrial poisons and is released with insulin.

Gerold M. Grodsky, PhD, professor of biochemistry of the University of California, San Francisco, School of Medicine, described work he and Miss Barbara Frankel did on the perfused pancreas of Chinese hamsters. In this animal, as in man, diabetes develops in a pattern indicating genetic transmission. Nine generations of glycosuric brother-sister matings produced hamsters which were homozygous for 90 percent of the genetic traits examined. These animals also showed no intragroup skin transplant rejection. Non-ketotic animals were mated and 20 percent of the offspring showed ketosis and diabetes, 50 percent were non-ketotic and diabetic, 10 percent had minimal glycosuria, and the remaining 20 percent were aglycosuric, but had a high frequency of glucose intolerance. Orci, in Geneva, has found that in the pancreatic islets of diabetic Chinese hamsters alpha cells are increased in number. Studies were done to compare the responses of the isolated perfused pancreas of non-ketotic diabetic Chinese hamsters to aglycosuric littermates. The studies showed that following a glucose challenge, the two phases of insulin release occurred in the normal time pattern, but were only half as great in the diabetic animals as in the controls. The pancreas of diabetic hamsters also had higher baseline glucagon levels, which were poorly suppressed by high perfusate glucose concentrations. In the diabetic pancreas arginine was a poor stimulator of insulin release, but a strong stimulator of glucagon release. Theophylline produced similar insulin and glucagon responses in both diabetic and aglycosuric pancreas. Though the pancreas of some diabetic animals had either a normal insulin or glucagon response to glucose, in none were both hormone responses normal. The insulin-glucagon ratio following glucose was found to separate the responses of islets from diabetic hamsters almost completely from those of controls.

Rachmiel Levine, MD, executive medical director, City of Hope, Duarte, California, briefly described current work by Robert Seecof, of that institution, on the effect of insulin on muscle and myoneural cell cultures of drosophila, the fruit fly, an invertebrate organism which does not produce insulin. Insulin added to these cultures produced cell growth, cell proliferation, and increased cell fat. A substance immunologically similar to pork insulin was found in larval drosophila tissue. A structural similarity between insulin and vertebrate nerve growth factor, a locally active substance important in embryonic development, has also been observed. In discussion, the possibility that these three substances could be evolutionary products of a primitive growth-related material was mentioned.

Edward R. Arquilla, MD, PhD, professor and chairman of the Department of Pathology, University of California, Irvine, California College of Medicine, related the structure of the insulin molecule to its biologic function. The structural detail of the insulin molecule has been determined by using x-ray diffraction. Crystalline insulin is a hexamer consisting of three dimers. In solution, insulin is usually monomeric. Dimerization occurs only at concentrations greater than 50 μg per ml and involves a specific surface of the insulin molecule. Previous molecular modification studies have shown that the small size of the N-terminal amino acid of the A-chain (glycine) and the area of the B-chain adjacent to tyrosine A-19 are important to insulin's biologic function.

Dr. Arquilla reported additional information about insulin structure-function relations gained using immunologic techniques. Insulin may be measured by using immune hemolysis as well as

by the usual insulin radioimmunoassay. In immune hemolysis, stable insulin competes with insulin-coated erythrocytes for anti-insulin antibodies which, if attached to the erythrocytes, induce hemolysis. It has been found that a number of insulin derivatives will react quite differently with the same antiserum in the two systems, indicating that the antibodies important to the two assays react to separate portions of the insulin molecule. Radioimmunoassay antibodies appear to be directed predominantly to the area of the A-chain involved in dimerization. Antibodies important to the immune hemolysis system are directed to other areas of the insulin molecule. Antibodies to insulin derivatives have been shown to have unique properties in these assays. Antisera to desalanine-desasparagine insulin, a biologically inactive derivative, react in the radioimmunoassay and not in immune hemolysis. They have been found to neutralize insulin *in vivo* better than antisera to insulin itself, suggesting that the dimerization site may be involved in insulin's biologic activity.

The invited lecturer, David M. Kipnis, MD, chairman of the Department of Medicine of Washington University School of Medicine in St. Louis, spoke on his studies of hypoglycemia, the autonomic nervous system, and insulin production by the pancreas. He first reported studies on a group of reactive hypoglycemic patients in whom late hypoglycemia regularly developed but whose glucose tolerance was otherwise within normal limits. These persons regularly had high 30-minute and 60-minute serum glucose levels, suggesting rapid glucose absorption from the stomach. Indium 113 was used to examine their rate of gastric emptying, which was found to be normal. However, when glucose was instilled directly into the duodenum rather than ingested, their serum glucose rise was more rapid than that of normal controls. Moderate doses of phenformin stopped this rapid serum glucose rise and also reduced the insulin response and prevented the late hypoglycemia which would otherwise occur. It was not clear whether phenformin changed the secretion of insulin or reduced the rate of glucose uptake.

Cholinergic blockade was also effective in treatment of reactive hypoglycemia. An unusual patient with long-standing symptomatic postprandial hypoglycemia had a strikingly elevated insulin response to oral glucose which became normal following propantheline. In fasting, the insulin response to a glucose load is characteristically blunted. A small amount of food preceding the load will restore the insulin response to normal. An inducible glucoreceptor substance in the beta cells is one explanation of this phenomenon. Beta methylglucoside and phloridzin (phloretin-betaglucoside) have been found to stimulate insulin secretion in isolated rat islets. The structural similarity of these substances is further evidence for a glucoreceptor. Lectins are plant proteins which react with substances on animal cell surfaces. Of a large group of plant lectins, only mushroom phytohemagglutinin (PHA) effectively stimulated insulin secretion. It also produced glucagon release from the pancreas and growth hormone release from the pituitary. Mushroom PHA binds to a specific glycopeptide on the cell surface. Its half saturation binding concentration, 2.9×10^{-7} moles per liter, is the same as that required for it to produce half-maximal insulin release. A mushroom PHA concentration sufficient to stimulate insulin release did not increase conversion of glucose to carbon dioxide; calcium was not required for its action. Mushroom PHA appears to be a useful new tool for studying membrane phenomena involved in the secretory process.

John W. Farquhar, MD, associate professor of medicine, Stanford University School of Medicine, discussed the relation between atherosclerosis and diabetes. There is an increased prevalence of coronary heart disease in both males and females whose response to a glucose load is above the 80 percentile for their age. Other kinds of vascular diseases and blood pressure elevation are also associated with marginal glucose tolerance. Blood lipid elevation may contribute to the observed relation between atherosclerosis and diabetes. In patients with severe diabetes, when blood insulin is low, a decline in lipoprotein lipase produces increased serum lipid levels. A different situation is present in mild diabetes. Overproduction, rather than impaired clearance, produces elevated lipid level. Obesity has an effect unrelated to blood sugar level. In childhood-onset obesity, there is a pronounced increase in the body's total number of fat cells. In adult-onset obesity, fat cell number does not change, so that fat cell size is often decidedly increased. The oversized adipocyte is particularly resistant to insulin action. This insulin resistance may generate a hyperinsulinism which in turn leads to overproduction hyperlipemia. Weight reduction causes diminution in adipose cell size, leading to

reduced insulin resistance and decline in plasma triglyceride and cholesterol levels. Predilection to atherosclerosis may well be decreased by the fall in insulin level associated with weight loss.

Gerald M. Reaven, MD, professor of medicine, Stanford University School of Medicine, summarized his group's studies on the role of insulin in protein synthesis by rat liver. They produced insulin deficiency in two ways—using either alloxan or streptozotocin to destroy the islet cells, or administering anti-insulin serum to neutralize circulating insulin. When animals were studied 48 to 72 hours after the onset of diabetes from the insulin deficiency, protein synthesis was decidedly inhibited regardless of the cause of insulin deficiency. Insulin-deficient liver was found to have a reduced amount of rough endoplasmic reticulum, decreased glycogen content, and enlarged mitochondria. Pronounced differences in protein synthetic activities of the two hepatic ribosomal populations were found. Free ribosomes, unchanged in number, had increased protein synthetic activity. Bound ribosomes were decreased both in number and in protein synthetic activity per milligram of RNA. These changes in bound and free ribosome content and activity were not seen in the livers of growth-hormone deficient diabetic rats. They could also be prevented by insulin administration. The effect of more chronic insulin deficiency on rat liver metabolism was also studied. Protein synthesis by bound ribosomes was restored in seven days; after 28 days it achieved supernormal levels. The protein synthetic activity of free ribosomes remained unchanged in chronic insulin deficiency. The effect of insulin deficiency on hepatic protein synthesis clearly varied with the duration of insulin deficiency.

Donald E. McMillan, MD, director of diabetes research of the Sansum Medical Research Foundation, Santa Barbara, reviewed the potential importance of blood viscosity changes in the development of diabetic microangiopathy. Serum viscosity, increased in both early and late diabetes, is more elevated in diabetic persons who have evidence of microangiopathy—retinopathy, neuropathy, or nephropathy. Extent of microangiopathy is positively correlated with serum viscosity elevation. The major cause of increased serum viscosity is altered serum protein composition. Changes in serum protein synthesis by the liver appear to account for the viscosity increase. Many serum proteins have altered levels in diabetes suggesting that the serum viscosity elevation might be a nonspecific result of altered liver metabolism. When individual protein levels were compared with severity of microangiopathy, it was found that only proteins closely related to viscosity were also directly related to sequelae. The close relation between protein changes increasing viscosity and microangiopathy suggests that altered blood viscosity may play a direct role in producing microcirculatory failure in diabetes. Erythrocyte aggregation is known to be increased in diabetes and the serum viscosity changes may contribute to erythrocyte aggregation. A flow model analysis of the effect of erythrocyte aggregation on blood flow in small tubes indicates that erythrocyte aggregation does not directly impair flow. The viscosity of the peripheral fluid after the aggregates form is lower than that of the original fluid. If erythrocyte aggregation is important in producing diabetic microangiopathy, it must interact to obstruct flow with other factors such as local vessel narrowing.

The following participated in valuable discussions which are not possible to report here: John H. Karam, MD, assistant director, Metabolic Research Unit, University of California, San Francisco School of Medicine; Victor R. Lavis, MD, assistant professor of medicine, University of Washington School of Medicine; Leona V. Miller, MD, associate professor of medicine, University of Southern California School of Medicine; I. Arthur Mirsky, MD, professor of medicine and psychiatry, University of California, Los Angeles School of Medicine; Mark A. Sperling, MD, assistant professor of pediatrics, University of California, Los Angeles School of Medicine; J. C. Sodoyez, MD, research investigator, Orange County Medical Center, Orange; Arne N. Wick, PhD, professor of biochemistry, California State University, San Diego; and Robert H. Williams, MD, professor of medicine, University of Washington School of Medicine.

Perhaps the most impressive element of the conference was the growing diversity of approaches utilized by the investigators in their efforts to improve our understanding of diabetes mellitus and the metabolic and hormonal changes associated with it.

in memoriam

Adams, Robert Malcolm, San Leandro. Died July 23, 1974 in San Leandro of myocardial infarction, aged 58. Graduate of University of Southern California School of Medicine, Los Angeles, 1941. Licensed in California in 1941. Dr. Adams was a member of the Alameda-Contra Costa Medical Association.

Carlin, Gene Arnold, Los Angeles. Died August 24, 1974 in Los Angeles of heart disease, aged 54. Graduate of Southwestern Medical School of the University of Texas, Dallas, 1949. Licensed in California in 1951. Dr. Carlin was a member of the Los Angeles County Medical Association.

Clay, Ernest H., Montebello. Died August 4, 1974 in Petaluma, aged 80. Graduate of Rush Medical School, Chicago, 1926. Licensed in California in 1944. Dr. Clay was a member of the Los Angeles County Medical Association.

Cunningham, Robert Arthur, Pasadena. Died July 21, 1974 in Pasadena, aged 69. Graduate of the Univerity of Kansas School of Medicine, Lawrence-Kansas City, 1931. Licensed in California in 1932. Dr. Cunningham was a member of the Los Angeles County Medical Association.

Eccleston, John Oliver, Stockton. Died August 14, 1974 in Stockton, aged 66. Graduate of St. Louis University School of Medicine, 1934. Licensed in California in 1936. Dr. Eccleston was a member of the San Joaquin County Medical Society.

Frees, Benjamin Marsh, sr., Los Angeles. Died August 27, 1974 in Los Angeles of heart disease, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1914. Licensed in California in 1914. Dr. Frees was a member of the Los Angeles County Medical Association.

Hackett, Arthur Bailey, Sacramento. Died August 15, 1974 in Sacramento, aged 55. Graduate of the University of Southern California School of Medicine, Los Angeles, 1950. Licensed in California in 1950. Dr. Hackett was a member of the Sacramento County Medical Association.

Iki, George S., Sacramento. Died September 1, 1974 in Kingsberg of heart disease, aged 81. Graduate of the University of California Medical School, Berkeley-San Francisco, 1921. Licensed in California in 1921. Dr. Iki was a member of the Sacramento County Medical Association.

Kringel, Alan, Menlo Park. Died August 3, 1974 in Palo Alto of heart disease, aged 55. Graduate of Columbia University College of Physicians and Surgeons, New York, 1943. Licensed in California in 1955. Dr. Kringel was a member of the Santa Clara County Medical Society.

Lachman, George S., San Francisco. Died August 4, 1974 in San Francisco, aged 75. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1923. Licensed in California in 1929. Dr. Lachman was a member of the San Francisco Medical Society.

McGovney, Richard B., Santa Ana. Died April 26, 1974 of heart disease, aged 71. Graduate of State University of Iowa College of Medicine, Iowa City, 1926. Licensed in California in 1928. Dr. McGovney was a retired member of the Santa Barbara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Piser, Alfred L., San Bernardino. Died April 8, 1974 of myocardial infarction, aged 64. Graduate of the University of Illinois College of Medicine, Chicago, 1935. Dr. Piser was a member of the Riverside County Medical Association.

Sundberg, Rudolph Herbert, San Diego. Died August 29, 1974, aged 73. Graduate of the University of Nebraska College of Medicine, Omaha, 1925. Licensed in California in 1929. Dr. Sundberg was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

104th Annual Session
AND
Western Scientific Assembly

FEBRUARY 21-26, 1975 • THE BILTMORE HOTEL and LOS ANGELES CONVENTION CENTER

PLAN TO ATTEND THE PROGRAMS and VISIT THE EXHIBITS

Among the topics:

☐ 9th ANNUAL CANCER SYMPOSIUM
Cancer: A Potpourri of Progress

☐ OCCUPATIONAL HEALTH CONFERENCE
The Physician and CalOSHA

☐ MEDICINE AND RELIGION CONFERENCE
Physicians and Clergymen Look at Homosexuality

☐ PEER REVIEW CONFERENCE
Ambulatory Care Review

☐ SPECIAL CONFERENCE
Third Congress on Health of the School Age Child

☐ SPECIAL CONFERENCE
Keeping Abreast of RVS

☐ SPECIAL CONFERENCE
Your Computer vs. Theirs

☐ SPECIAL CONFERENCES ON
Pharmacy and Therapeutics, Environmental Health, Venereal Disease, Alcoholism and Other Drug Dependencies, Government and Medicine

☐ SPECIALTY SECTION MEETINGS
Allergy, Anesthesiology, Chest Diseases, Dermatology, General/Family Practice, General Surgery, Industrial Medicine/Surgery, Internal Medicine, Neurology, Nuclear Medicine, Obstetrics/Gynecology, Ophthalmology, Orthopedics, Otolaryngology, Pathology, Pediatrics, Physical Medicine/Rehabilitation, Plastic Surgery, Preventive Medicine/Public Health, Psychiatry, Radiology, Urology

45th Annual Convention—Woman's Auxiliary to California Medical Association

California Medical Association—House of Delegates

FOR ACTION IN 1975

Three Constitutional amendments were introduced in the 1974 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates, and must be published twice before they come before the House of Delegates for action.

ARTICLE III, PART B, SECTION 9. COMPOSITION

Introduced by: Council
Representing: Council
Author: E. Kash Rose, MD

Constitutional Amendment No. 1-74
Committee G

Resolved: That Article III, Part B.—Council.—Section 9.—Composition be amended by deleting the words in brackets and adding the words in italics, so that this section shall now read:

The Council shall consist of:

(a) Elected councilors from the councilor districts set forth in Section 10. Each councilor district shall be entitled to elect one councilor for each 1,000 active members, or major fraction thereof, according to its membership as of the first day of September of the preceding year; provided, that each councilor district shall be entitled to a minimum of one councilor.

(b) Elected councilors from any one district shall not, at any time, exceed 40 percent of the total Council membership.

(c) The president, president-elect, immediate past president,[10] speaker and vice-speaker.

[(d) The secretary, *who shall be selected from the Council* and editor, when they are members of the Association, shall be ex officio members of the Council without the right to vote.[11]]

[e] *(d)* The editor, when [they are members] *he is a member* of the Association, shall be *an* ex officio member[s] of the Council without the right to vote.

[f] *(e)* One member of the Executive Committee of the Scientific Board, who shall be elected by the Scientific Board from representatives of the scientific sections or members-at-large, who shall be an ex officio member of the Council with the right to vote.

ACTION: Tabled for one year; to be acted upon at the 1975 meeting of the House of Delegates.

ARTICLE III, PART B, SECTION 11. ELECTION OF COUNCILORS

Introduced by: Council
Representing: Council
Author: E. Kash Rose, MD

Constitutional Amendment No. 2-74
Committee G

Resolved: That Article III, Part B, Section 11, be amended, to read:

District councilors shall be elected [by vote of the delegates from each district] in the manner and at the time specified in the Bylaws; provided, however, that at the first meeting of the House of Delegates after a district councilor has been selected, his name shall be submitted to the House by the delegates from the district, and (1) if there is no challenge by any delegate then the speaker shall declare his election completed, and (2) if any delegate shall challenge the election on any ground, including fitness of the nominee of the district to serve as a district councilor, the questions presented by the challenge shall be submitted to a Qualifications Committee consisting of the president, president-elect and one delegate, appointed by the speaker, from the councilor district involved. The Qualifications Committee shall consider all grounds upon which the nominee is challenged and report back to the House. If the committee reports in favor of confirming the nominee's election, the speaker shall declare him elected. If the committee reports against confirming the nominee's election, a three-fourths (¾) affirmative vote shall be necessary to sustain the report of the committee, in which event the nominee shall be ineligible to serve as district councilor and the delegates from the district shall immediately proceed to the selection of another nominee for the vacant office. If an adverse report of the Qualifications Committee is not sustained then the nominee shall be declared elected by the speaker.

ACTION: Tabled for one year; to be acted upon at the 1975 meeting of the House of Delegates.

* * *

ARTICLE III, PART B, SECTION 12. COUNCILORS: TERMS OF OFFICE

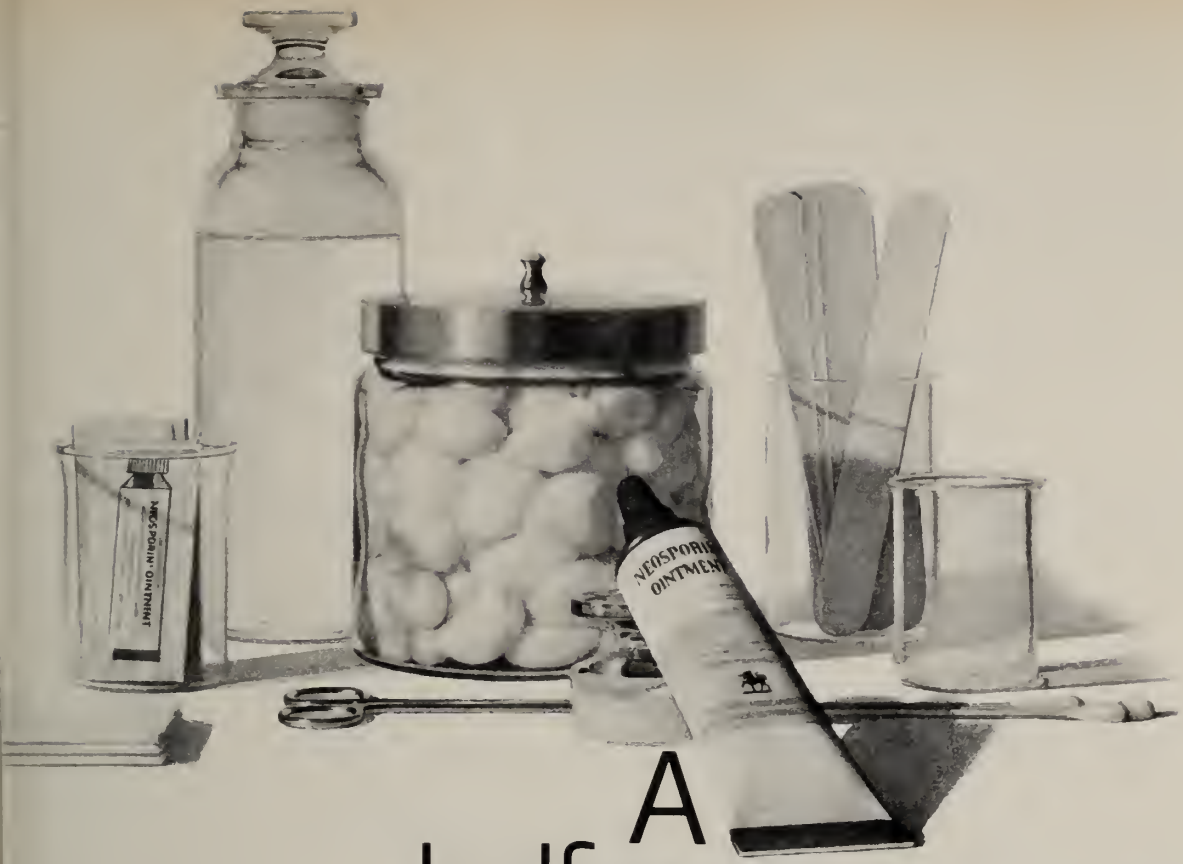
Introduced by: Council
Representing: Council
Author: E. Kash Rose, MD

Constitutional Amendment No. 3-74
Committee G

Resolved: That Article III, Part B, Section 12, be amended, to read:

Section 12. Councilors: Terms of Office. Councilors shall serve for terms of three (3) years; [one-third (⅓) to be elected in each year] except that the initial term of a new office arising hereunder may be for less than three (3) years, as the Bylaws may provide, to allow for staggering of terms. A councilor shall not serve more than three (3) consecutive terms of office.

ACTION: Tabled for one year; to be acted upon at the 1975 meeting of the House of Delegates.



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use of the potential hazard of nephrotoxicity and ototoxicity n, care should be exercised when using this product in treating s, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

HANDBOOK OF POISONING—Diagnosis & Treatment—Eighth Edition—Robert H. Dreisbach, MD, PhD, Clinical Professor of Environmental Health, School of Public Health and Community Medicine, University of Washington, Seattle, and Professor (Emeritus) of Pharmacology, Stanford University School of Medicine. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 517 pages, $6.50.

INDUSTRIAL PHARMACOLOGY—Volume I: Neuroleptics—Edited by Stuart Fielding, PhD, Head, Psychopharmacology Section, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey; and Harbans Lal, PhD, Professor of Pharmacology, Toxicology and Psychology, University of Rhode Island, Kingston. Futra Publishing Company, 295 Main Street, Mount Kisco, NY (10549), 1974. 349 pages, $19.50.

LUPUS ERYTHEMATOSUS—A Review of the Current Status of Discoid and Systemic Lupus Erythematosus and Their Variants—Second Edition—Edited by Edmund L. Dubois, MD, Associate Clinical Professor of Medicine, University of Southern California School of Medicine; Director of the "Collagen Disease" Clinic, Los Angeles County/University of Southern California Medical Center, Los Angeles. University of Southern California Press, Los Angeles, CA (90007), 1974. 798 pages, $36.00 plus $1.50 shipping in the U.S. and 6% Sales Tax for California residents. NOTE: copies or further information can be obtained by contacting the editor directly at the following address: Edmund L. Dubois, MD, Editor, 435 North Bedford Drive, Beverly Hills, CA 90210.

THE NEW PHYSICIAN SURGICAL QUIZ—Terrence S. Carden, Jr., MD, Director of Publications, Student American Medical Association, Editor, THE NEW PHYSICIAN, Rolling Meadows, Ill., Director of Emergency Services, Highland Park Hospital Foundation, Highland Park, Ill. Appleton-Century-Crofts/New York, A Publishing Division of Prentice-Hall, Inc., 292 Madison Avenue, New York City (10017), 1974. 431 pages, $12.50.

OBSTETRICS AND GYNECOLOGY ANNUAL—1974—Volume 3—Editor: Ralph M. Wynn, MD, Professor and Head, Department of Obstetrics and Gynecology, The Abraham Lincoln School of Medicine, University of Illinois at the Medical Center, Chicago. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1974. 564 pages, $18.50.

PILLS, PROFITS, AND POLITICS—Milton Silverman, PhD, Research Pharmacologist and lecturer in pharmacology, University of California, San Francisco; and Philip R. Lee, MD, Professor of social medicine, University of California, San Francisco. University of California Press, 2223 Fulton Street, Berkeley, CA (94720), 1974. 421 pages, $10.95.

PROCEEDINGS OF THE SECOND INTERDISCIPLINARY SYMPOSIUM ON GENDER DYSPHORIA SYNDROME—Edited by Donald R. Laub, MD, Associate Professor of Surgery, Chief, Division of Rehabilitation Surgery; and Patrick Gandy, MS, Chief, Gender Identity Program, Stanford University School of Medicine. Division of Plastic Surgery, R213, Stanford University Medical Center, Stanford, CA (94305), 1974. 243 pages, $10.00 (prepaid).

PSYCHOSOCIAL BASIS OF MEDICAL PRACTICE—An Introduction to Human Behavior—Charles L. Bowden, MD, Associate Professor, Department of Psychiatry, The University of Texas Health Science Center at San Antonio Medical School; and Alvin G. Burstein, PhD, Professor and Chief, Division of Psychology, Department of Psychiatry, The University of Texas Health Science Center at San Antonio Medical School. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore, MD (21202), 1974. 229 pages, $7.95.

QUESTIONS AND ANSWERS ON DEATH AND DYING—Elizabeth Kübler-Ross, MD. Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1974. 177 pages, $4.95 (Hardcover); $1.50 (Paperback).

RESPIRATORY GAS EXCHANGE AND BLOOD FLOW IN THE PLACENTA—Proceedings of a Symposium in Conjunction with the XXV International Congress of Physiological Sciences, Aug 4-6, 1971, Hannover, Germany—Editors: Lawrence D. Longo, MD, Departments of Physiology and Obstetrics and Gynecology, Loma Linda University, Loma Linda, CA; and Heinz Bartels, MD, Physiologisches Institut der Medizinischen Hochschule, Hannover. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, 1972. 570 pages, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. (20402). Price: $6.05, domestic postpaid, $5.50.

TREATMENT AND MANAGEMENT OF OBESITY—Edited by George A. Bray, MD, Professor of Medicine and Director of the Clinical Research Center, Harbor General Hospital, Torrance; and John E. Bethune, MD, Professor and Chairman, Department of Medicine, University of Southern California School of Medicine, Los Angeles. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Ave., Hagerstown, MD (21740), 1974. 160 pages, $5.95 (Paperback).

THE ULTIMATE STRANGER—The Autistic Child—Carl H. Delacato, ED D, Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 226 pages, $6.95.

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Precaution. As with all thyroid preparatio this drug will alter results of thyroid functi tests.
Adverse Reactions. Overdosage or too rap increase in dosage may result in signs a symptoms of hyperthyroidism, such as me strual irregularities, nervousness, cardiac rhythmias, and angina pectoris.
Dosage and Administration. Optimal dosa is usually determined by the patient's clinic response. Confirmatory tests include BMR, ^{131}I resin sponge uptake, T_3 ^{131}I red cell u take, Thyro Binding Index (TBI), and Achill Tendon Reflex Test. Clinical experience h shown that a normal PBI (3.5-8 mcg/100 r will be obtained in patients made clinica euthyroid when the content of T_4 and T_3 adequate. Dosage should be started in sm amounts and increased gradually with inc ments at intervals of one to two weeks. Us maintenance dose is 0.5 to 3.0 grains (32 190 mg) daily.
Overdosage Symptoms. Headache, instabil nervousness, sweating, tachycardia, with u usual bowel motility. Angina pectoris or co gestive heart failure may be induced aggravated. Shock may develop. Massive ov dosage may result in symptoms resembl thyroid storm. Chronic excessive dosage produce the signs and symptoms of hyperth roidism.
(Treatment: In shock, supportive measu should be utilized. Treatment of unrecogniz adrenal insufficiency should be considered.)
How Supplied. ¼ grain; ½ grain; scored grain; 1½ grain; scored 2 grain; 3 grain; a scored 5 grain tablets, in bottles of 100 a 1000.
Full information available on request.

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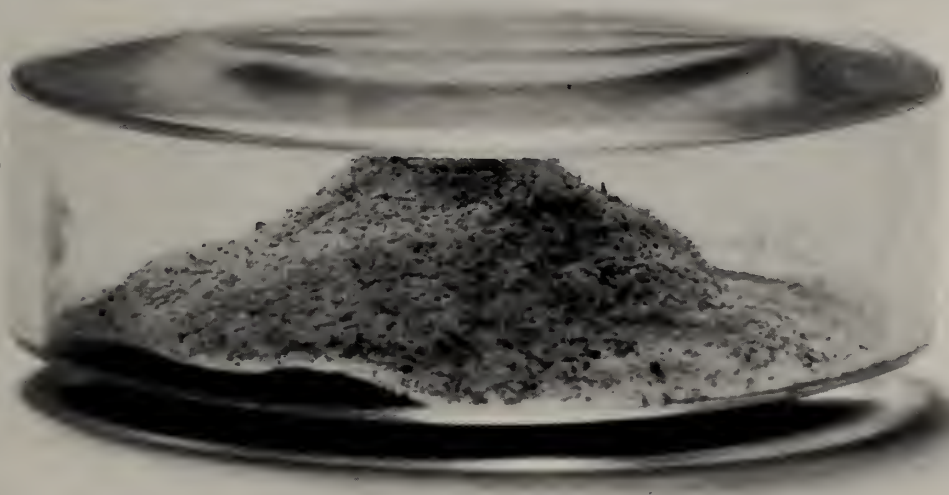

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PSYCHIATRISTS, GP'S for geriatric program within State hospital 50 miles north of Los Angeles. Fine climate near beaches. Salary $23,484 to $31,488. Optional monthly OD 5% extra. Other fringe benefits. Contact: Martin Gish, MD, Program Director (6G), Box A, Camarillo, CA 93010. Telephone (805) 482-4671, ext. 2638.

CARDIOLOGIST—Board certified internist with subspecialty in cardiology needed for busy cardiology practice in Orange County, with excellent facilities and adjacent medical school. Send résumé to Box 9392, Western Journal of Medicine, 731 Market St., San Francisco, 94103.

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(Continued on Page 36)

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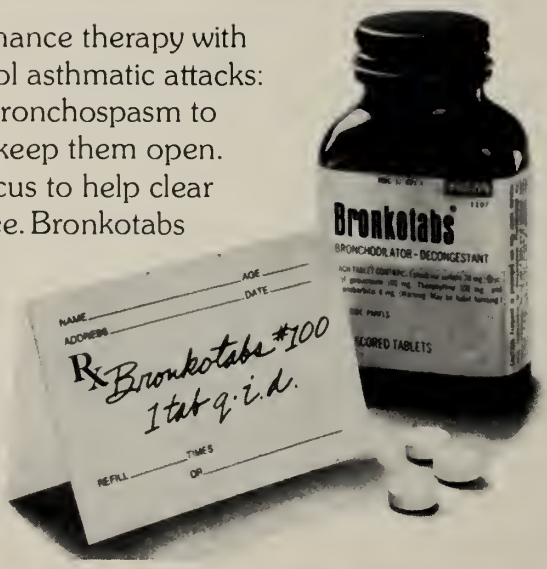

PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

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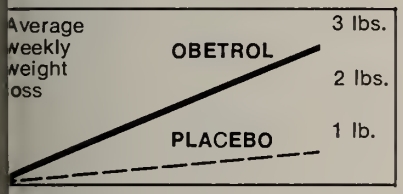

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Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

ctions: Amphetamines are sympathomimetic amines with NS stimulant activity. Peripheral actions include elevation of stolic and diastolic blood pressures and weak bronchodilator nd respiratory stimulant action. The anorectic effect diminishes ter a few weeks.

dications: Exogenous obesity, as a short term (a few weeks) djunct in a regimen of weight reduction based on caloric striction. For patients in whom obesity is refractory to other easures.

ontraindications: Advanced arteriosclerosis, symptomatic rdiovascular disease, moderate to severe hypertension, hyper-yroidism, known hypersensitivity or idiosyncracy to the mpathomimetic amines. • Agitated states. • Patients with a story of drug abuse. • During or within 14 days following the dministration of monoamine oxidase inhibitors, hypertensive ises may result.

arnings: Tolerance to the anorectic effect usually develops thin a few weeks. When this occurs, the recommended dose ould not be exceeded in an attempt to increase the effect, ther, the drug should be discontinued. Amphetamines may npair the ability of the patient to engage in potentially haz-rdous activities such as operating machinery or driving a motor hicle; the patient should therefore be cautioned accordingly.

recautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with e use of amphetamines and the concomitant dietary regimen. mphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or spensed at one time in order to minimize the possibility of verdosage.

dverse Reactions: *Cardiovascular:* Palpitation, tachycardia, evation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, emor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
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   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
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3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

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January 1973

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(Continued from Page 32)

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PHYSICIAN to direct County Child Health and Disability Prevention Program. Should have at least one year's experience in providing services to children or possess a graduate degree in Public Health. $30,000 per year plus travel. Contact Owen A. Kearns, MD, Kern County Health Officer, P.O. Box 997, Bakersfield, CA 93302; (805) 861-3655.

CLINIC DIRECTOR

WANTED: Physician to be director of a 100-patient Methadone Research Clinic. Experience with drug abuse problems. Salary $32,000 per year. Reply to Dr. Avram Goldstein, Addiction Research Foundation, 701 Welch Rd., Suite 325, Palo Alto, CA 94304.

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WANTED: ASSOCIATE FOR ALLERGY AND CLINICAL IMMUNOLOGY PRACTICE in North San Diego County. No investment necessary. Excellent opportunity for a young individual interested in growth. Box 9395, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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CARDIOLOGIST, 31 ABIM, University trained with experience directing active CCU desires group or hospital based practice with emphasis in non invasive areas. Write Box 9399 Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST—37 years, university trained, Board Certified AP-CP, excellent references, good experience, California licensed, wishes relocation in California. Apply Box 9401, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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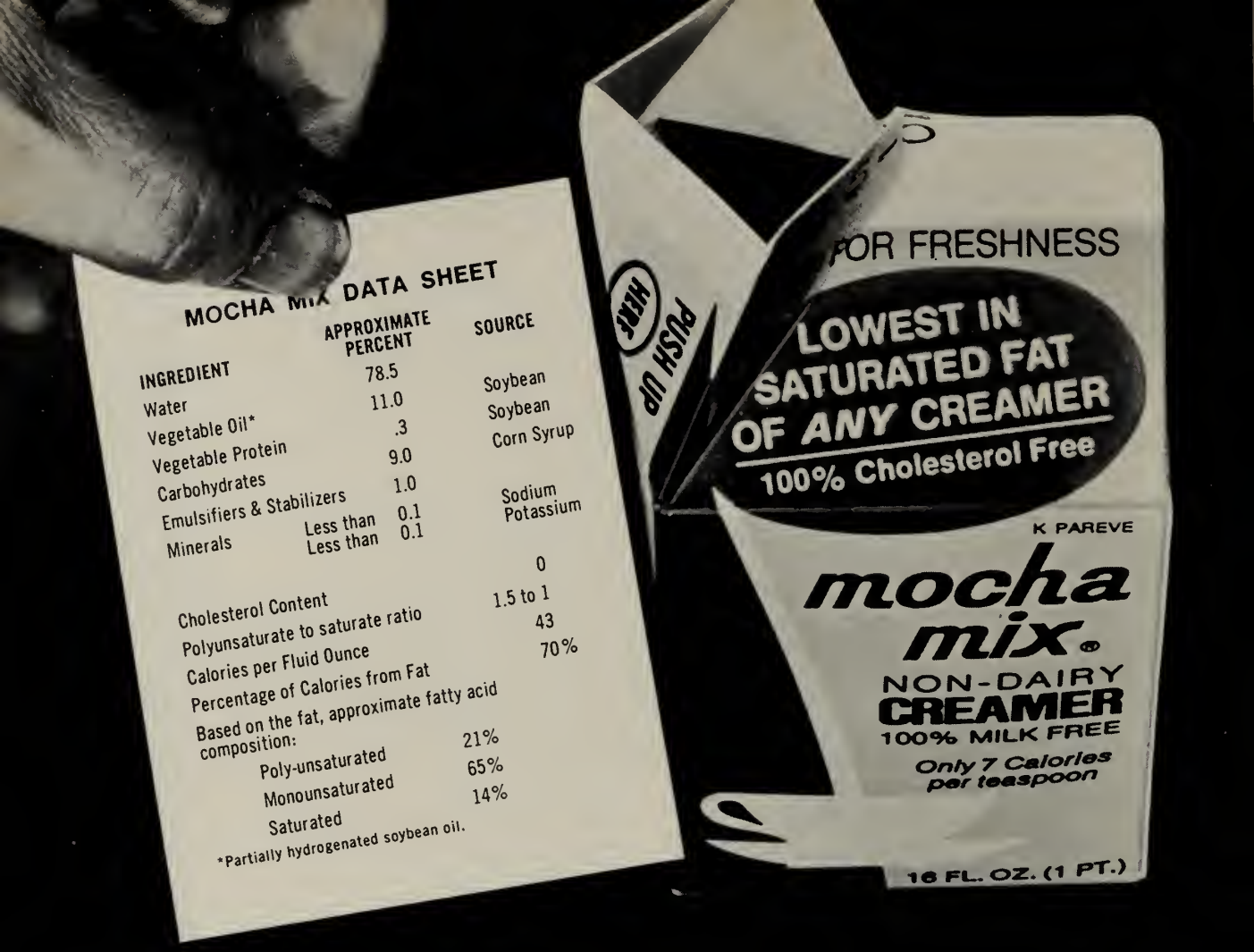

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COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

October 25—**Cause and Treatment of Leukemia.** Leukemia Society and UCSF at UCSF. Friday. 7 hrs. $25. Contact: Leukemia Society of America, Inc., Bay Area Chapter, 323 Geary St., San Francisco 94102.

November 2—**Tumors of the Head and Neck.** PMC. Sat.

November 11-12—**Franz Buschke Lectureship—2nd Annual.** UCSF. Monday-Tuesday. Nov. 11—Heavy Particle Radiation Therapy; Nov. 12—Hyperthermia in Cancer Therapy. Contact: Glenn E. Sheline, MD, Div. of Radiation Oncology, UCSF.

November 14-15—**Recent Advances in Hematology and Medical Oncology.** See Medicine, November 14-15.

November 15-16—**Current Concepts in the Diagnosis and Treatment of the Hidden Malignancies: The Intra-Abdominal Cancers.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. Contact: Dept. of Cont. Education, Mt. Zion Hospital, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 108.

November 23—**Breast Cancer: Update 1974.** American Cancer Society, N. E. Los Angeles County Unit, at Huntington-Sheraton Hotel, Pasadena. Saturday. 6 hrs. $20. Contact: Hilario R. Liras, Ed. Dir., ACS, 230 N. Lake Ave., No. 1, Pasadena 91101. (213) 795-7774.

December 8—**Slide Seminar on Tumors of the Gastro-Intestinal Tract.** California Tumor Tissue Registry at Century Plaza Hotel, Los Angeles. Sunday. Contact: Weldon K. Bullock, MD, Exec. Dir., Calif. Tumor Tissue Registry, L.A. County/USC Medical Ctr., 1200 N. State St., Box 40, L.A. 90033. (213) 225-3131, ext. 71820.

Continuously—**Tumor Conference.** Cruden Education Center, St. John's Hospital, Oxnard. Fridays, 12:00 noon-1:00 p.m. Advice and consultation from specialists in surgical, medical, radiotherapeutic, chemotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Cancer program has 3 year accreditation from American College of Surgeons. Contact: D. Gordon Johnston, MD, Dir. of Med. Ed., St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 266.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists (UCLA faculty members) in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John R. Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

October 16—**A Look at the Lung—1974.** N. T. Enloe Memorial Hospital, Chico Community Mem. Hospital, Lung Assn. of Superior Calif., Butte-Glenn Med. Soc., at Holiday Inn, Chico. Wednesday. $20. Contact: Mr. John Behrman, Cont. Ed. Program, N. T. Enloe Mem. Hosp., 5th Ave. & The Esplanade, Chico 95926.

October 17-20—**California Society of Internal Medicine—Annual Meeting.** Ahwahnee Hotel, Yosemite. Thursday-Sunday. 8 hrs. Contact: Carol H. Handley, Exec. Dir., CSIM, 1412 Central Towers, 703 Market St., San Francisco 94103. (415) 362-1548.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

October 18—**Recent Advances in Rheumatology.** UCD at Woodlake Inn, Sacramento. Friday.

October 18-19—**San Diego County Heart Association.** Sheraton-Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Mrs. Cathy Ware, Prog. Dir., SDCHA, 3640 Fifth Ave., P.O. Box 3625, San Diego 92103. (714) 291-7454.

October 24-26—**Non-Invasive Cardiovascular Procedures.** USC. Thursday-Saturday.

October 24-26—**West Coast Allergy Society—13th Annual Scientific Program.** St. Francis Hotel, San Francisco. Thursday-Saturday. 19 hrs. $25 for members; $30 non-members. Contact: Daniel K. Billmeyer, MD, Prog. Chr., 2164 S.W. Park Pl., Portland 97205. (503) 226-1555.

October 25-26—**Clinical Gastroenterology.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. Contact: Williamson B. Strum, MD, Div. of Gastroenterology, Scripps Clinic & Research Foundation, 476 Prospect St., La Jolla 92037.

October 25-26—**Rheumatology.** Southern Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

October 26—**Emergency Respiratory Care for Health Related Professions.** PMC. Saturday.

November 2-3—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

November 4-13—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

November 4-December 2—**Dermatology Seminars.** UCSF at Sheraton Inn, Fresno. Mondays, 7:00-9:00 p.m. $50 for five sessions; $10 individual sessions.

November 6—**Infectious Diseases Seminar—3rd Annual.** Torrance Memorial Hospital at Sheraton Inn Hotel, Los Angeles. Wednesday. $50. Contact: Torrance Memorial Hospital, 3330 Lomita Blvd., Torrance 90509. (213) 325-9110, ext. 362.

November 8—**Developments in the Diagnosis of Contact Dermatitis.** UCSF. Friday.

November 8-10—**Practical Electrocardiography—"Chung's Approach."** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Sunday. $125. Contact: Donald K. Chung, MD, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

November 11-15—**Pediatric Allergy and Clinical Immunology.** See Pediatrics, November 11-15.

November 13-14—**Coronary Care.** USC. Wednesday-Thursday.

November 14-15—**Recent Advances in Hematology and Medical Oncology.** UCLA at Holiday Inn, Los Angeles. Thursday-Friday.

November 16-17—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

November 17—**Veterinary Dermatology Seminar.** STAN. Sunday.

November 20-22—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

November 22—**Complications of Diabetes Mellitis—Pathophysiology and Management.** UCI at VA Hospital, Long Beach. Friday. 6 hrs.

November 23—**Update: Advances in Medical and Surgical Care of the Coronary Patient.** Inter-Hospital Council for Continu-

(Continued on Page 42)

Whenever an APC/narcotic is indicated.

Percodan® Tablets ©

Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning May be habit forming), 0.38 mg. oxycodone terephthalate (Warning May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS: *Drug Dependence:* Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Percodan, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, Percodan is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Percodan should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Percodan may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Percodan should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children: Percodan should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Percodan or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: Percodan should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS: The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. The usual adult dose is one tablet every six hours as needed for pain.

DRUG INTERACTIONS: The CNS depressant effects of Percodan may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE: *Signs and Symptoms:* Serious overdose with Percodan is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of Percodan may, in addition, result in acute salicylate intoxication.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530
DU PONT

Pain: a call to action.

- rapid acting
- effective, reliable oral analgesia in moderate to moderately severe pain
- oxycodone, the principal ingredient of Percodan, is one of the more readily absorbed oral narcotic analgesics
- one tablet q.6 h.*

Tablets
Percodan® C

Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

See facing page for Brief Summary

*See dosage and administration section of Brief Summary

Whenever an APC/narcotic is indicated.

6581

(Continued from Page 40)

ing Medical Education of the San Gabriel-Pomona Valleys at Kellogg West Conference Facility, Cal Poly, Pomona. Saturday. $60. Contact: Donald Adams, Admin., Foothill Presbyterian Hospital, Grand Avenue, Glendora 91740.

November 30-December 1—**Physiology of Respiration.** UCSF. Saturday-Sunday.

December 2-6—**Advances in Diagnosis and Treatment in Clinical Medicine.** American College of Physicians, UCLA, and Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Friday. $140 for ACP members; $200 non-members. Contact: ACP, Registrar, Postgraduate Courses, 4200 Pine St., Philadelphia, Pa. 19104. (215) 222-8120.

December 5-7—**Advances in Heart Disease 1975.** American College of Cardiology at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

December 11—**Colloquia in Cardiology—No. 7: Echocardiography.** American College of Cardiology at Ambassador Hotel, Los Angeles. Wednesday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

December 11-13—**Exercise in Heart Disease.** USC at Honolulu. Wednesday-Friday.

December 14-15—**Kidney Function.** UCSF. Saturday-Sunday.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Cardiology Conference/General Medical Conference.** Cruden Education Center, St. John's Hospital, Oxnard. Tuesdays, 12:00 noon-1:00 p.m. Conferences including case presentations, discussions of specific cardiology and medical problems. Contact: R. E. Liguori, MD, Dir. of Cardiovascular Laboratory, St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 256.

Continuously—**Cardiology Conferences.** San Diego County Heart Association at Sharp Hospital, San Diego. Fridays, 8-10 a.m. Contact: William Kuzman, MD, Sharp Hospital, 7901 Frost St., San Diego. (714) 277-6121. Or Mrs. Cathy Ware, SDCHA, P.O. Box 3625, San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 294-5663. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conference.** Thursdays, 8:00 p.m. **Cardiosurgical Conference.** Fridays, 2:00 p.m. UCSD at University Hospital, San Diego.

Continuously—**Medical Mortality Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Fridays, 11:30 a.m.

Continuously—**Medical Chest Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

Continuously—**Medical-Surgical G.I. Conference.** UCSD at University Hospital, 3rd floor, rm 3, San Diego. Tuesdays, 12:30 p.m.

Continuously—**Hematology Pathology/Hematology Morphology Conference.** Mondays, 11:00 a.m. **Hematology Clinical Conference.** Mondays, 12 noon. UCSD alternating between University and VA Hospitals, San Diego.

Continuously—**Gastroenterology Conference.** Tuesdays, 11:00 a.m. **Gastrointestinal Conference.** Tuesdays, 12:30 p.m. **Gastroenterology-Pathology Conference.** Wednesdays, 11:00 a.m. UCSD at University Hospital, San Diego.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Preceptorships in Cardiology.** PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Continuously—**Preceptorships in Practical Office Dermatology.** PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Continuously—**Preceptorships in Infectious Disease.** PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Renal Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

Continuously—**Rheumatology Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. 2nd and 4th Fridays, 12:30 p.m.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of every other month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1534.

Continuously—**Training for Physicians in General Internal Medicine.** LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Dermatology. 11:00 a.m. VA Hospital, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

8:30 a.m., Auditorium, Brown Bldg., Mt. Sinai Hospital, Los Angeles. UCLA.

Dermatology. 10:00 a.m. University Hospital, San Diego. UCSD.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:00 noon. Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., VA Hospital, San Diego. UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:00-10:00 a.m., 4th Floor, UCLA Medical Center. UCLA.

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30-10:00 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

October 14-15—**New Horizons in Perinatal Intensive Care.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. 13 hrs. $125. Contact: Bonnie Stapleton, Cont. Ed. Coord., Harbor Gen. Hosp., 1124 W. Carson, Torrance 90502. (213) 775-7711, ext. 1373.

October 15-18—**Ob-Gyn Review.** USC. Tuesday-Friday.

October 20-23—**International Family Planning Research Association.** Gene Autry Hotel, Palm Springs. Sunday-Wednesday. Contact: Ludwig Lauerhass, Exec. Dir., 2960 W. 8th St., Los Angeles 90005. (213) 386-1970.

November 1—**Advances in Perinatal Care.** Northern California Obstetrical & Gynecologic Society at Host Airport Hotel, Sacramento. Friday. Contact: Solon Barbis, MD, Prog. Chr., 1816 Professional Dr., Sacramento. (916) 482-6510.

November 6-9—**American College of Obstetricians & Gynecologists, District VIII.** Century Plaza Hotel, Los Angeles. Wednesday-Sunday. Will reconvene Nov. 11-13 at Princess Hotel, Acapulco. Contact: ACOG District VIII, 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

November 22-25—**1974 Symposium of Gynecologic Endoscopy.** American Association of Gynecological Laparoscopists at Disneyland Hotel, Anaheim. Friday-Monday. Contact: Jordan M. Phillips, MD, 11239 S. Lakewood Blvd., Downey 90241. (213) 862-8181.

December 2-6—**Family Planning.** UCLA. Monday-Friday. Contact: Irvin M. Cushner, MD, Ob-Gyn Dept., UCLA Center for Health Sciences, L.A. 90024. (213) 825-1046.

Continuously—**Ob-Gyn Case Review.** Saturdays, 8:00 a.m. **Gyn Tumor Conference/Mortality Conference.** Wednesdays, 12:30 p.m. **Ob-Gyn Pathology Conference.** Wednesdays, 4:00 p.m. UCSD at University Hospital, San Diego.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

8:00-9:00 a.m., Fourth Floor Auditorium, UCLA Medical Center. UCLA.

5:00 p.m. Pickard Auditorium, University Hospital, San Diego. UCSD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

PEDIATRICS

October 14-15—**New Horizons in Perinatal Intensive Care.** See Obstetrics and Gynecology, October 14-15.

October 18-19—**Society for Ear, Nose, and Throat Advances in Children.** See Surgery, October 18-19.

(Continued on Page 46)

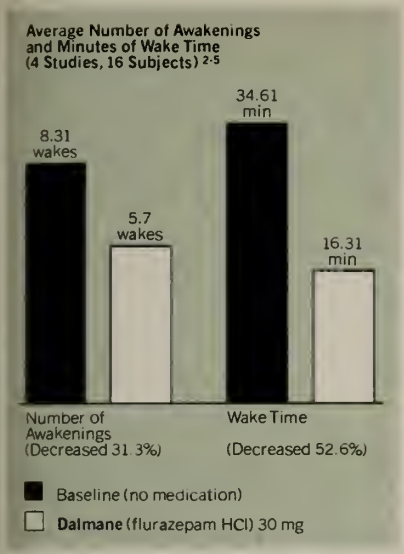
sleep is usually maintained with fewer nighttime awakenings...

a consistent benefit of

Dalmane®

(flurazepam HCl) proved by a 17-night clinical study in the sleep research laboratory evaluating effectiveness in insomnia patients[1]

Eight patients received no medication on nights 1-4; Dalmane (flurazepam HCl) or placebo on nights 5-9; crossover capsule, nights 10-14; and no medication, nights 15-17. While placebo had no significant effect on sleep maintenance, Dalmane reduced nighttime awakenings by 55.1% when given on nights 5-9, 43.7% on nights 10-14. When four control subjects received placebo on the 10 "drug" nights, awakenings *increased* 11.5% over baseline.[1]



confirmed by clinical studies in four geographically separated sleep research laboratories[2-5]

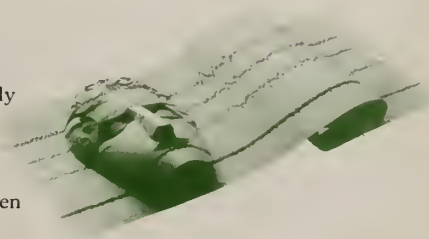
Using a 14-night protocol, involving eight insomniac and eight normal subjects, four studies confirmed the sleep-maintaining effectiveness of Dalmane (flurazepam HCl) and the reproducibility of this response. On average, one 30-mg capsule reduced number of awakenings by 31.3% and wake time by 52.6%. In all these studies, Dalmane induced sleep rapidly, on average within 17 minutes; reduced nighttime awakenings; and provided, on average, 7 to 8 hours of sleep without repeating dosage.[2-5]

Dalmane (flurazepam HCl) induces and maintains sleep, with relative safety

Dalmane is generally well tolerated; morning "hang-over" has been relatively infrequent. While dizziness, drowsiness, lightheadedness and the like have been noted most often, particularly in the elderly and debilitated, physicians should be aware of the possibility of more serious reactions, as noted in the Complete Product Information.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.
Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.



when restful sleep is indicated

Dalmane®
(flurazepam HCl)

One 30-mg capsule *h.s.* — usual adult dosage (15 mg may suffice in some patients).
One 15-mg capsule *h.s.* — initial dosage for elderly or debilitated patients.

- **induces sleep within 17 minutes, on average**
- **reduces nighttime awakenings**
- **sustains sleep 7 to 8 hours, on average, without repeating dosage**

REFERENCES: 1. Kales J, *et al*: *Clin Pharmacol Ther 12*:691-697, Jul-Aug, 1971
2. Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-7, 1971
3. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ
4. Vogel GW: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ
5. Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ

ROCHE

ROCHE LABORATORIES
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Nutley, New Jersey 07110

(Continued from Page 43)

October 19-23—**American Academy of Pediatrics.** Hilton Hotel, San Francisco. Saturday-Wednesday. Contact: Robert G. Frazier, MD, Exec. Dir., 1801 Hinman Ave., Evanston, Ill. 60204.

November 11-15—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

December 7—**American Academy of Pediatrics, Chapter I, District IX.** San Franciscan-PSA Hotel, San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501. (415) 523-3417.

Continuously—**Fellowship in Cleft Palate.** See Surgery, Continuously.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD. Small Conference Room, University Hospital, San Diego. Fridays, 12:30 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., and Fridays, 9:30-11:00 a.m., Conference Room 3. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Fourth Thursday of each month, 2:00 p.m., Main Doheny Conference Room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Continuously—**Pediatric Immunology and Allergy Seminar.** UCSD. Wednesdays, 8:00 a.m.

Continuously—**Pediatric Neurology.** UCSD at University Hospital, 3rd floor, rm. 3, San Diego. 1st and 3rd Wednesdays, 12:30 p.m.

Continuously—**Pediatric-Radiology-Urology Conference.** UCSD at University Hospital, Radiology Conference Room, San Diego. 1st and 3rd Fridays, 4:00 p.m.

Grand Rounds—Pediatrics

Tuesdays

Pediatric Cardiology. 7:30 a.m. University Hospital, San Diego. UCSD.

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Pediatric Infectious Disease. 1:30 p.m. University Hospital, San Diego. UCSD.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:30 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m. 5th floor Ward, St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

October 24-27—**American Academy of Child Psychiatry.** Fairmont Hotel, San Francisco. Thursday-Sunday. Contact: American Academy of Child Psychiatry, 1800 R Street, NW, Washington, D.C. 20009.

November 7-8—**Community Alternatives to State Hospital Treatment.** UCD. Thursday-Friday.

December 13—**Psychological Aspects of the Rehabilitation of Patients with Industrial Back Injuries.** PMC. Friday.

Continuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Seminar in Ambulatory Methods.** UCSD Mental Health Clinic, San Diego. Mondays, 11:00 a.m.

Continuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

Grand Rounds—Psychiatry

Tuesdays

8:30 a.m. VA Hospital, Rm. 2010, San Diego. UCSD.

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

RADIOLOGY AND PATHOLOGY

October 19—**Fluid & Electrolyte Symposium.** St. Mary Medical Center, Long Beach. Saturday. 6 hrs. $50. Contact: Dept .of Medical Education, St. Mary Medical Center, P.O. Box 887, 1050 Linden Ave., Long Beach 90801. (213) 435-4441, ext. 425.

October 25-26—**Society of Nuclear Medicine, Northern & Southern California Chapters—Annual Meeting.** Hilton Hotel, San Francisco. Friday-Saturday. Contact: Society of Nuclear Medicine, No. Calif. Chapter, 1595 Soquel Dr., Santa Cruz. (408) 476-7300.

November 2—**Laboratory Evaluation of Thyroid Diseases.** PMC. Saturday.

November 2-3—**Evaluation of Clinical Laboratory Instrumentation.** UCSF. Saturday-Sunday.

November 9-10—**Adult Cardiac Radiology.** UCLA. Saturday-Sunday.

November 11-12—**Franz Buschke Lectureship.** See Cancer, November 11-12.

November 16-17—**American Association for Electromyography and Electrodiagnosis.** St. Francis Hotel, San Francisco. Saturday-Sunday. Contact: W. C. Wiederholt, MD, Sec., 7010 Via Valverde, La Jolla 92037. (714) 459-8443.

Continuously—**Nuclear Medicine Conference.** Radiology Classroom, St. John's Hospital, Oxnard. Mondays, 12:00 noon-1:00 p.m. Cases reviewed and discussed. Advice and consultation from specialists in the practice of nuclear medicine techniques. Contact: Michael Lopiano, MD, Dir. of Nuclear Med. Dept., St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 297.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward I. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Continuously—**Medical X-Ray Conference.** Monday-Friday, 9:30 a.m. (Wednesdays, 8:30 a.m.). **Diagnostic X-Ray Review.** Wednesdays, 3:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Radiology/Pathology Conference.** UCSD at University Hospital, Pickard Amphitheatre, San Diego. Thursdays, 12:30 p.m.

Continuously—**G.I. Radiology Conference.** Fridays, 1:00 p.m. **Pediatric Radiology Conference.** Thursdays, 4:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Neuroradiology Conference.** UCSD at University Hospital, San Diego, Tuesdays, 4:30 p.m. and at VA Hospital, San Diego, Wednesdays, 2:00 p.m.

Continuously—**Ortho-Radiology Conference.** UCSD at VA Hospital, San Diego. Fridays, 8:00 a.m.

Continuously—**Radiology-Urology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 3:30 p.m.

Continuously—**Pathology Review.** Wednesdays, 9:30 a.m. **Cardiovascular Pathology Conference.** Tuesdays, 8:00 a.m. **Pathology-Urology Conference.** Alternate Mondays, 4:30 p.m. UCSD at University Hospital, San Diego.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

October 17-18—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 17-19—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

October 18-19—**Society for Ear, Nose, and Throat Advances in Children.** Hilton Hotel, San Francisco. Friday-Saturday. Contact: Jack L. Paradise, MD, Sec.-Treas., 125 De Soto St., Pittsburgh, Pa. 15213.

October 19—**Surgical Anatomy and Surgery of Total Hip Replacement.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital, L.A., Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Ed. Committee, ICS, 5351 Tampa Ave., Tarzana 91356. (213) 344-3305.

October 28-November 1—**Association of Military Surgeons of the United States—81st Annual Meeting.** Town and Country Hotel, San Diego. Monday-Friday. Contact: Lt. Commander Thomas E. Thomas. MSC USN, Military Personnel Dept., Naval Regional Medical Center, San Diego 92134. (714) 233-2022.

October 31-November 1—**Strabismus.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday.

November 7-8—**Sterling Bunnell Memorial Lecture—Surgery of the Hand and Upper Extremity.** UCSF. Thursday-Friday. Contact: Ms. Leslie J. Williams, U-471, UCSF. (415) 666-1166.

November 8—**Orthopedic Symposium—Arthroplasties of the Knee.** Southern Calif. Permanente Medical Group at Sheraton Hotel, Anaheim. Friday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., L.A. 90027. (213) 667-4242.

November 9—**Orthopaedic Surgery and Surgical Anatomy of the Lower Extremity.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital, L.A., Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Ed. Committee, ICS, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

November 14-15—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

November 14-16—**Phaco-Emulsification.** St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

November 16—**Intraocular Lens Implant Conference—Current Status and Analysis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. $100. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

November 16-17—**American Society of Anesthesiologists—Regional Refresher Course.** Riviera Hotel, Palm Springs. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068.

November 20-23—**Western Surgical Association—Annual Meeting.** Union Square Hyatt, San Francisco. Wednesday-Saturday. Contact: William P. Mikkelson, MD, 1127 Wilshire Blvd., Los Angeles 90017.

November 21-23—**Management of Acute Hand Injuries.** USC and American Academy of Orthopaedic Surgeons at USC. Thursday-Saturday. Contact: USC or Arthur H. Osborne, MD, 3314 Rancho Rio Bonita Rd., Covina 91724.

November 23—**Anesthesia Postgraduate Seminar—Pain, Drug Abuse and Their Management.** UCD at Woodlake Inn, Sacramento. Saturday.

November 23—**Update: Advances in Medical and Surgical Care of the Coronary Patient.** See Medicine, November 23.

December 4-6—**Advise and Dissent in Glaucoma—Annual Ophthalmology Course.** UCSF at Union Square Hyatt, San Francisco. Wednesday-Friday.

December 6-8—**Electronystagmography.** PMC at Sheraton Palace Hotel, San Francisco. Friday-Sunday.

December 11-14—**Fluorescein Angiography and Photocoagulation in Macular and Retinal Vascular Disease.** USC. Wednesday-Saturday.

December 12-13—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

December 12-14—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

December 14—**Orthopaedic Surgery and Surgical Anatomy of the Neck and Upper Extremity.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. $50. 8 hrs. Contact: Irving Rehman, PhD, Chairman, Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

December 15—**Clinical Disorders of the Pelvis.** UCLA an Granada Community Hospital at Calif. State Univ., North ridge. Sunday. Contact: Rose Degraffenreid, Granada Com munity Hosp., 10445 Balboa Blvd., Granada Hills 91344 (213) 360-1021, ext. 730.

Continuously—**Fellowship in Cleft Palate.** Rancho Los Amigo Hospital, Downey. One-year fellowship in the total evaluatio and management of cleft lip and cleft palate patients. Con tact: Libby Wilson, MD, Rancho Los Amigos Hosp., 760 E. Imperial Highway, Downey 90242. (213) 922-7454.

Continuously—**Anesthesia Lecture Series.** UCSD at Universit Hospital, 3rd floor conference room, San Diego. Wednes days, 4:45 p.m.

Continuously—**Anesthesiology Mortality and Morbidity Con ference.** UCSD at VA Hospital, Rm. 6006, San Diego Thursdays, 4:30 p.m.

Continuously—**Neurological Sciences.** St. Francis Hospita Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of radic logical evaluations and pathological specimens of currer material and review of current topics in specialty. Weekl notification of cases available. Contact: Ralph Miller, Ad min. Asst., St. Francis Hospital, 3630 Imperial Highwa Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Science Lecture Series.** Dept. of Surger St. Mary's Hospital, San Francisco. Mondays, 11:15 a.m 12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgo MD, Dir. of Medical Education, St. Mary's Hospital, 220 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Pos graduate traineeships of 4-14 days duration, as you wish. N tuition but donations accepted. Contact: Orthopaedic Div sion, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at S Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser Sa Francisco, and Harkness Memorial Hospitals. Third Tue day of each month, 6:00 p.m. Contact: Charles H. Lithgo MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes S San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at L Angeles County-USC Medical Center. Mondays, 7:00-9: p.m. Contact: Dept. of Orthopedics, USC School of Me 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. I arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCS By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arrang ment.

Continuously—**Training for Physicians in Nephrology.** CRM Area VI and LLU at LLU. Courses of four weeks or mo available, to be scheduled by arrangement. Hemodialys peritoneal dialysis, renal biopsy, and kidney transplantati 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, S Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Cla room. Contact: Charles H. Lithgow, MD, Dir. of Med. E St. Mary's Hospital, 2200 Hayes St., San Francisco 941 (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, S Francisco. Mondays, 1:30 p.m., Morrissey Hall. Conta Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's H pital, 2200 Hayes St., San Francisco 94117. (415) 752-40

Continuously—**Surgical Morbidity and Mortality Conferen** 4th Monday of each month, 9:00-10:00 a.m., Morrissey H Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., Mary's Hospital, 2200 Hayes St., San Francisco 94117. (4 752-4000.

Continuously—**Surgical Mortality and Morbidity Conference.** UCSD alternating between University and VA Hospitals, San Diego. Saturdays. 9:30 a.m.

Continuously—**Ortho Surgical Conference.** UCSD at University Hospital, 3rd floor conference room, San Diego. Wednesdays, 8:00 a.m.

Continuously—**Otolaryngology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Fridays, 8:30 a.m.

Continuously—**Laryngeal Physiology.** UCSD at VA Hospital, San Diego. Fridays, 8:30 a.m.

Continuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Trauma Conference.** UCSD at University Hospital, 1st floor conference room, San Diego. Tuesdays, 3:30 p.m.

Continuously—**Vascular Surgery Conference.** UCSD alternating between VA and University Hospitals, San Diego. Thursdays, 4:00 p.m.

Continuously—**Radiology-Urology Conference. Pathology-Urology Conference.** See Radiology and Pathology, Continuously.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Lebanon Hall Auditorium, Cedars-Sinai Hospital, Los Angeles. UCLA.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery.** 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Otolaryngology. 12:00 noon. University and VA Hospitals, San Diego. UCSD.

Neurology, Neuropathology, Neurosurgery. 4:00 p.m. University and VA Hospitals, San Diego. UCSD.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital, 1st, 3rd, 5th Sat.; VA Hospital, 2nd, 4th Sat., San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

Orthopedic Surgery. 8:00-9:00 a.m. UCSF. September 21-June 14, 1975. Subjects to be announced.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

October 14-17—**American Academy of Family Physicians—Annual Scientific Assembly.** Los Angeles Convention Center. Monday-Thursday. Contact: Edward E. Daleske, Sec., Comm. on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, Mo. 64114. (816) 333-9700.

October 18—**Dimensions of Human Relatedness.** Kings View Hospital at Towne House, Fresno. Friday. $35. Contact: Julie Fernandez, Kings View Hospital, 42675 Road 44, Reedley 93654.

October 19—**Fluid and Electrolyte Symposium.** St. Mary Medical Center, Long Beach. Saturday. 6 hrs. $50. Contact: Dept. of Medical Education, St. Mary Medical Center, P.O. Box 887, 1050 Linden Ave., Long Beach 90801. (213) 435-4441, ext. 425.

October 19-20—**Origin of Sex and Reproduction.** University Extension at 145 Dwinelle Hall, U.C., Berkeley. Saturday-Sunday. Contact: Nathan W. Cohen, PhD, Dir., Curriculum Development in Science, UC Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1061.

October 23—**Ethical Aspects of Experimentation with Human Subjects.** USC. Wednesday.

October 28-November 1—**Intensive Care.** STAN. Monday-Friday.

October 28-November 1—**Hawaii Medical Association.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: Mr. H. Tom Thorson, Exec. Dir., 510 S. Beretania St., Honolulu 96813.

November 1-2—**Thy Brother's Keeper.** USC. Friday-Saturday.

November 1-3—**The Patient—Our Ultimate Concern.** Calif. Society of Hospital Pharmacists, Calif. Hospital Assn., CMA, Calif. Nursing Assn., Calif. Pharmaceutical Assn. at Marriott Hotel, Los Angeles. Friday-Sunday. Contact: Kenneth N. Horowitz, Pharm. D., Centinela Valley Community Hospital, 555 E. Hardy St., Inglewood 90301.

November 3-6—**American Society of Tropical Medicine and Hygiene—23rd Annual Meeting.** Princess Kaiulani, Honolulu. Sunday-Wednesday. Contact: George R. Healy, PhD, P.O. Box 15208, Druid Hills Branch P.O., Atlanta, Ga. 30333. (404) 633-3311, ext. 3227.

November 6—**Infectious Diseases Seminar.** See Medicine, November 6.

November 10-13—**California Academy of Family Physicians.** Hyatt Regency Hotel, San Francisco. Sunday-Wednesday. Contact: William W. Rogers, Exec. Sec., CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 11-22—**Emergency Department Medicine in Practice.** Harbor General Hospital, UCLA, American College of Emergency Physicians at Harbor General Hospital, Torrance. Two weeks. $450. Contact: Mrs. Bonnie Stapleton, Cont. Ed. Coord., Professional Staff Assn., Harbor Gen. Hosp., 1124 W. Carson St., Torrance 90502.

November 12—**Medical Seminar—10th Annual: Problem Oriented Medical Records.** Pacific Hospital of Long Beach. Tuesday. $60. Contact: Laura Tondreault, Dir., Community Relations, Pacific Hospital, 2776 Pacific Ave., P.O. Box 1268, Long Beach 90801.

November 17-22—**American Congress of Rehabilitation Medicine.** St. Francis Hotel, San Francisco. Sunday-Friday. Contact: Creston C. Herold, Exec. Dir., ACRM, 30 N. Michigan Ave., Chicago 60602.

November 19—**Association of Academic Physiatrists.** St. Francis Hotel, San Francisco. Tuesday. Contact: George H. Kraft, Sec., Dept. of Rehabilitation Medicine, Univ. of Washington, Seattle 98195.

November 23—**Anesthesia Postgraduate Seminar—Pain, Drug Abuse and Their Management.** See Surgery and Anesthesiology, November 23.

November 29-December 1—**International College of Applied Nutrition—Fall Seminar.** International Hotel, Palm Springs. Friday-Sunday. Contact: Michael Walczak, MD, P.O. Box 386, La Habra 90631. (213) 697-4576.

December 5-6—**Air Pollution Medical Research Conference.** American Medical Association at Sheraton Palace Hotel, San Francisco. Thursday-Friday. Contact: AMA, 535 N. Dearborn St., Chicago, Ill. 60610.

December 7—**Family Practice Symposium.** Southern California Permanente Medical Group at San Diego. Saturday. Contact: Barbara King, Dept. of Research & Education, Rm. 6014, Kaiser-Permanente, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

December 27-28—**Symposium on Innovations in Athletic Conditioning and Sports Medicine—2nd Annual.** University Extension at UC, Berkeley. Friday-Saturday. 15 hrs. $50. Contact: Nathan W. Cohen, PhD, Dir., Curriculum Development in Science, UC Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1061.

Continuously—**Psychiatric Seminars for Physicians.** San Francisco Psychoanalytic Institute, San Francisco. 1st and 3rd Thursdays, October-May, 1975; 8:00 p.m. Invitations to all non-psychiatric physicians of 9 Bay Area counties. Contact: Jerome D. Oremland, MD, Chr., Extension Division, S. F. Psychoanalytic Institute, 2420 Sutter St., San Francisco 94115. (415) 931-4205.

Continuously—**Emergency Care.** USC. September 17-December 3. Tuesdays, 7:30-10:00 p.m.

Continuously—**Bedside Clinics.** USC. September 26-December 19. Thursdays, 7:30-9:30 p.m.

Continuously—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. October 1-December 3. Tuesdays (except Nov. 5 and 12).

Continuously—**Clinical Conferences.** UCSF at Community Hospital, Santa Cruz. October 9, 1974-June 11, 1975. Wednesdays.

Continuously—**Continuing Medical Education Noon Conferences.** The Hospital of the Good Samaritan, Los Angeles. Every weekday, 12-1 p.m. For monthly calendar, contact: Janie Sternal, Coord., Cont. Med. Ed., Hosp. of the Good Samaritan, 1212 Shatto St., Los Angeles 90029. (213) 482-8111.

Continuously—**Clinical Problems in Daily Practice: Physiological Basis and Practical Management.** UCSF at Chinese Hospital, San Francisco. 1st Tuesday of each month; 8:00-9:30 p.m. Sept.—Jaundice; Oct. & Nov.—to be announced.

Continuously—**Emergency Room Lecture Series.** UCSD at University Hospital, San Diego. Wednesdays, 10:00 a.m.

Continuously—**Endocrinology, Metabolism, Reproductive Medicine, Genetics Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 11:30 a.m

Continuously—**Preceptorships in International Health, Microbiology, Pharmacology and Experimental Therapeutics, Physiology.** UCSF. By special arrangement.

Continuously—**Family Health Program—Southern California** 2925 N. Palo Verde, Long Beach. Second Friday of eacl month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardin Chapter, American Academy of Family Physicians and UC at Ram's Horn Inn, San Bernardino. 3rd Thursday of eacl month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange Count Chapter, American Academy of Family Physicians at Saddle back Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheir Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comn Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comn Hosp., Baldwin Park; Huntington Intercomm. Hosp., Hun ington Beach; Imperial Gen. Hosp., Inglewood; La Habr Comm. Hosp.; La Mirada Comm. Hosp.; La Palma Inte community Hosp., La Palma; Los Alamitos Gen. Hosp.; Mi sion Comm. Hosp., Mission Viejo; Palm Harbor Hosp Garden Grove; Riviera Hosp., Torrance; Rio Hondo Men Hosp., Downey; San Gabriel Valley Comm. Hosp., Sa Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp Norwalk; West Anaheim Gen. Hosp.; Westminster Comn Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Portervil State Hospital. Contact: Frank McCarry, MD, P.O. B 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Cente** PMC and Sonoma Valley Hospital at Sonoma Valley Ho pital, Sonoma. Second Monday of each month in Dini Room of the hospital, 8:00-10:00 p.m. $100 per series, $ per session. Contact: William J. Newman, MD, 280 Perki St., Sonoma 95476. (707) 996-2165.

Continuously—**Basic Science Seminar.** UCSD Wednesday 9:15 a.m., University Hospital of San Diego County, S Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit su sidiary of CMA. Twice-a-month tape recorded summaries leading national meetings and surveys of current literatu Services by subscription in: Family Practice, Surgery, I ternal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthe ology, Ophthalmology, Otorhinolaryngology. Catalog of l tures and panel discussions in all areas of medical pract also available. $75 per year. Contact: Mr. Claron L. Oakl Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 900 (213) 483-3451.

Continuously—**Medical Media Network.** Programs and stu guides produced in association with faculties of major me cal schools and centers throughout the U.S. MMN a ministered by University Extension, UCLA. Rental or p chase, 16 mm, super 8 mm, videotape and video-casset Provides physicians with current educational programs. C tact: Ms. Jan MacAllister, Distribution Mgr., MMN, 109 Le Conte Ave., Room 540, Los Angeles 90024. (213) 8 7781.

Continuously—**Stanford-Mills Memorial Hospital Continu Education Program.** STAN at Mills Memorial Hospital, S Mateo. Tuesday-Friday weekly. Basic Science for the Cl cian, Grand Rounds, Intensive Care. Contact: STAN.

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COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

OF INTEREST TO ALL PHYSICIANS

October 16-19—**American Society of Human Genetics,** Portland. Contact: W. E. Nance, MD, Medical Genetics, Indiana University Medical Center, Indianapolis, IN 46202.

November 7—**Thrombophlebitis and Thromboembolic Disease,** 9:00 a.m. to 3:30 p.m. Assembly Hall, Portland Adventist Hospital. Contact: Theodore R. Flaiz, MD, Portland Adventist Hospital, 6040 S.E. Belmont, Portland, 97215.

November 30-December 4—**American Medical Association Clinical Meeting,** Portland. Contact: Ernest B. Howard, MD, AMA, 535 N. Dearborn Avenue, Chicago, IL 60610.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

October 24-25—**Office Management of Chronic Pain.** Seattle. 14 hrs. $95. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

November 7-9—**Advances in Internal Medicine.** Thursday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 16 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext 470.

November 14-15—**Drug Therapy.** Thursday-Friday, Seattle. 12 hrs. $50. Contact: Mr. Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 15-16—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. No fee. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext 470.

November 21-22—**Workshop for the Critically Ill Patient.** Thursday-Friday. Olympic Hotel and Harborview Medical Center, Seattle. $45 for physicians, $30 for nurses and other health professionals. Contact: Mr. Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

December 5-6—**Hypertension.** Thursday-Friday. Seattle. 12 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, 98195. (206) 543-1050.

January 16-17—**What's New in Pediatrics '75.** Thursday-Friday. Seattle. Fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

Ayerst Laboratories
Premarin 8, 9
Bio-Science Laboratories
Laboratory 19
Books Received 30
Breon Laboratories Inc.
Bronkotabs 34
Burroughs Welcome Co.
Empirin Compound with Codeine 6
Neosporin Ointment 29
Classified 32, 36
Compton Foundation 32
Dairy Council of California 16
Dorsey Laboratories
Triaminic Syrup 26
Triaminic Expectorant 37
Endo Laboratories
Percodan 40, 41
Lakeside Laboratories, Inc.
Norpramin 10, 11
Eli Lilly and Company
Keflex 28
Loma Linda Foods
Soyalac 5
Mead Johnson Laboratories
Vasodilan ..... 4th Cover
Merck Sharp & Dohme
Triavil 20, 21, 22
Obetrol Pharmaceuticals
Obetrol 35
Pharmaceutical Manufacturers Association
Prescription Ads 2, 3
Presto Food Products Inc.
Mocha Mix 38
PVO International Inc.
Saffola 15
A. H. Robins Company
Dimetapp/Phenaphen 17, 18
Roche Laboratories
Bactrim 12, 13, 14
Dalmane 44, 45
Librium ..... 2nd Cover and Page 1
G. D. Searle & Co.
Lomotil ..... 52 and 3rd Cover
Security Pacific Bank 27, 33
State Compensation Insurance Fund 23
Smith, Kline & French Laboratories
Dyazide 7
Warner-Chilcott Laboratories
Proloid 30, 31
Wyeth Laboratories
Bicillin/Wycillin 24, 25

January 22-24—**Advances in Neurology.** Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 18 hrs. $100, ACP members; $150, non-members; $50, ACP Associates. Contact: M. H. Jackson, Registrar, Postgraduate Courses, American College of Physicians, 4200 Pine St., Philadelphia, Pa., 19104.

January 24-25—**Tax, Estate and Financial Planning for Physicians.** Friday-Saturday. Seattle. Fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

January 26-February 1—**Advances in Perinatology.** Sunday-Saturday. Sun Valley, Idaho. 37½ hrs. $100 for physicians, $30 for nurses and other health professionals. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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Lomotil retarded gastrointestinal motility particularly during the first three hours after administration. It continued its moderating action on the bowel for at least three hours more.

Physicians prescribe Lomotil more often than any other drug when the urgency for the control of diarrhea is most distressing.

1. *Demeulenaere, L.: Action du R 1132 sur le transit gastro-intestinal, Acta Gastroent. Belg. 21:674-680 (Sept.-Oct.) 1958.*

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TABLETS/LIQUID

Each tablet and each 5 ml. of liquid contain:
diphenoxylate hydrochloride . . 2.5 mg.
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IMPORTANT INFORMATION: This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for meperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.

dications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

ntraindications: In children less than 2 years, due the decreased safety margin in younger age oups, and in patients who are jaundiced or hypersitive to diphenoxylate HCl or atropine.

rnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced patic disease or abnormal liver function tests, cause of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

*Dosage and administration: **Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid,* 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

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In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

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THE WESTERN Journal of Medicine

VOLUME 121 • NUMBER 5 **NOVEMBER 1974**

359 *Thyroid Nodules and Thyroid Cancer* FRANCIS S. GREENSPAN, MD

URINARY TRACT INFECTIONS IN CHILDREN

366 *Part I—Young Girls with Non-Refluxing Ureters*
WILLIAM R. FAIR, MD, DUNCAN E. GOVAN, MD, PhD, GERALD W. FRIEDLAND, MD, and ROY A. FILLY, MD

374 *Part II—Roentgenologic Aspects*
ROY A. FILLY, MD, GERALD W. FRIEDLAND, MD, DUNCAN E. GOVAN, MD, PhD, and WILLIAM R. FAIR, MD

382 *Part III—Treatment of Ureterovesical Reflux*
DUNCAN E. GOVAN, MD, PhD, WILLIAM R. FAIR, MD, GERALD W. FRIEDLAND, MD, and ROY A. FILLY, MD

SPECIALTY CONFERENCE

390 *Bacteriology of the Gut and Its Clinical Implications*
Moderator: JAMES S. CLARKE, MD; Discussants: JOHN G. BARTLETT, MD, SYDNEY M. FINEGOLD, MD, SHERWOOD L. GORBACH, MD, and SAMUEL E. WILSON, MD
Interdepartmental Clinical Case Conference, UCLA School of Medicine, Wadsworth Veterans Administration Hospital and Sepulveda Veterans Administration Hospital

MEDICAL STAFF CONFERENCE

404 *Diabetic Microangiopathy* Discussion by MARVIN D. SIPERSTEIN, MD, PhD

413 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Preventive Medicine and Public Health*

421 EDITORIALS • *A Consensus at Last* • *Emergency Medicine* • *Human Gut Microecology* • *Thyroid Nodules and Thyroid Cancer* • *Patient Care Audit* • *The Fascinations and Frustrations of Diabetes Mellitus*

CASE REPORTS

428 *Stupor, Bradycardia, Hypotension and Hypothermia—A Presentation of Wernicke's Encephalopathy with Rapid Response to Thiamine* WILLIAM J. ACKERMAN, MD

430 *Chronic Leg Ulceration in a Patient with Leprosy* JOEL M. NOE, MD and JOAN BARBER, MD

433 LETTERS TO THE EDITOR

TRAUMA ROUNDS

435 *Evaluation of the Patient with Head Injury* Chief Discussant: JULIAN HOFF, MD

PROGRESS IN PUBLIC ACCOUNTABILITY

439 *Medical Audit in Action—Experience in a Regional Kidney Disease Program*
BENJAMIN H. BARBOUR, MD, MARK C. LAMBERT, MD, and STANLEY R. FISHER, MD

SPECIAL ARTICLE

443 *Medical Aspects of Adolescents Participating in Sports* SAMUEL HURWITZ, MD

448 *In Memoriam*

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According to her major
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r iety. But according to the
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e .ngs, part of the problem
n sound like depression.
T is because her problem,
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e ive anxiety, is often accom-
p ed by depressive symptom-
t ogy. Valium (diazepam)
a provide relief for both—as
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e :d, the depressive symp-
o s associated with it are also
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n e patient within a few
a rather than in a week or
two, although it may take longer in some patients. In addition, Valium (diazepam) is generally well tolerated; as with most CNS-acting agents, caution patients against hazardous occupations requiring complete mental alertness.

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For further information on this subject, the following references are provided:

1. Henry BW, *et al: Dis Nerv Syst 30*:675-679, Oct 1969.
2. Hollister LE, *et al: Arch Gen Psychiatry 24*:273-278, Mar 1971.
3. Claghorn J: *Psychosomatics 11*:438-441, Sept-Oct 1970.

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opics or anticonvulsants, consider
ully pharmacology of agents em-
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tion. Usual precautions indicated in
ts severely depressed, or with latent
ssion, or with suicidal tendencies.

Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

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Subscription prices, $8 ($9 for foreign countries); s dent subscription $4; single copies 80 cents.

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The Editorial Board will be glad to receive and con for publication letters containing information of ger interest to physicians or presenting constructive critic on issues of the day.

"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

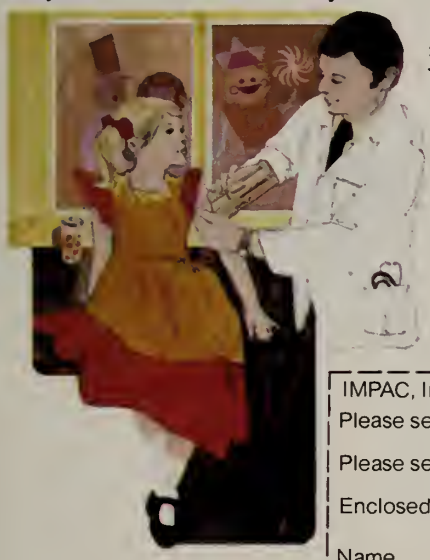
Neoject,
painless injection instrument that uses ordinary disposable syringes

Artist's concept of actual instrument

Neoject is a patented instrument that totally eliminates the pain of routine IM injections. This instrument is easy and rapid to use, and will be appreciated by all your patients. Controlled application of anesthetic at the injection site makes injections 100% painless. The syringe and needle are not visible to the patient in use, reducing the apprehension many patients feel toward injections.

*Model No. PI-100
U.S. Patent No. S,
3702608
3603742
Other U.S. & foreign patents applied for

Neoject uses standard 2.5 and 3cc disposable syringes, and may be used with any medication for IM injections. The instrument may be adjusted to administer any size dosage. Penetration depth is adjustable for 1/2 or 7/8 inch.



Neoject is a precision engineered instrument constructed of durable, non-corrosive, long lasting materials. The price of the instrument, including two anesthetic cartridges (enough for 125-150 injections each) with complete instructions is $89.00. Anesthetic refills are available in cartons of 12, or 24 at $2.00 per refill. Satisfaction guaranteed. If you are not completely satisfied after 30 days, return the instrument and your money will be refunded.

Just fill out the form below and mail to: IMPAC, Inc. P.O. Drawer D • Hospital Drive • Cleveland, Mississippi 38732.

IMPAC, Inc. • P.O. Drawer D • Hospital Drive • Cleveland, Mississippi 38732.

Please send _____ Neojects on your 30-day trial basis at $89.00 each.

Please send _____ Extra anesthetic refills at $2.00 each.

Enclosed is A Check A Money Order for $_____

Name_____

Address_____

City_____ State_____ Zip_____

I've enclosed $_____ (Includes postage, handling & tax) Allow 2-3 weeks for delivery

Sign of a cold* sufferer

Time for Ornade®

Each Spansule® capsule contains 8 mg. Teldrin®
(brand of chlorpheniramine maleate);
50 mg. phenylpropanolamine hydrochloride;
2.5 mg. isopropamide, as the iodide.

Fast relief of upper respiratory congestion and hypersecretion* with convenient b.i.d. dosage.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Indications**
Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Possibly effective: For relief of upper respiratory tract congestion and hypersecretion associated with vasomotor rhinitis and allergic rhinitis, and for prolonged relief.

Lacking in substantial evidence of effectiveness: For relief of nasal congestion and hypersecretion associated with the common cold and sinusitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hypersensitivity to any component; concurrent MAO inhibitor therapy; severe hypertension; bronchial asthma; coronary artery disease; stenosing peptic ulcer; pyloroduodenal or bladder neck obstruction. Children under 6.

Warnings: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Warn patients of possible additive effects with alcohol and other CNS depressants.

Usage in Pregnancy: In pregnancy, nursing mothers and women who might bear children, weigh potential benefits against hazards. Inhibition of lactation may occur.

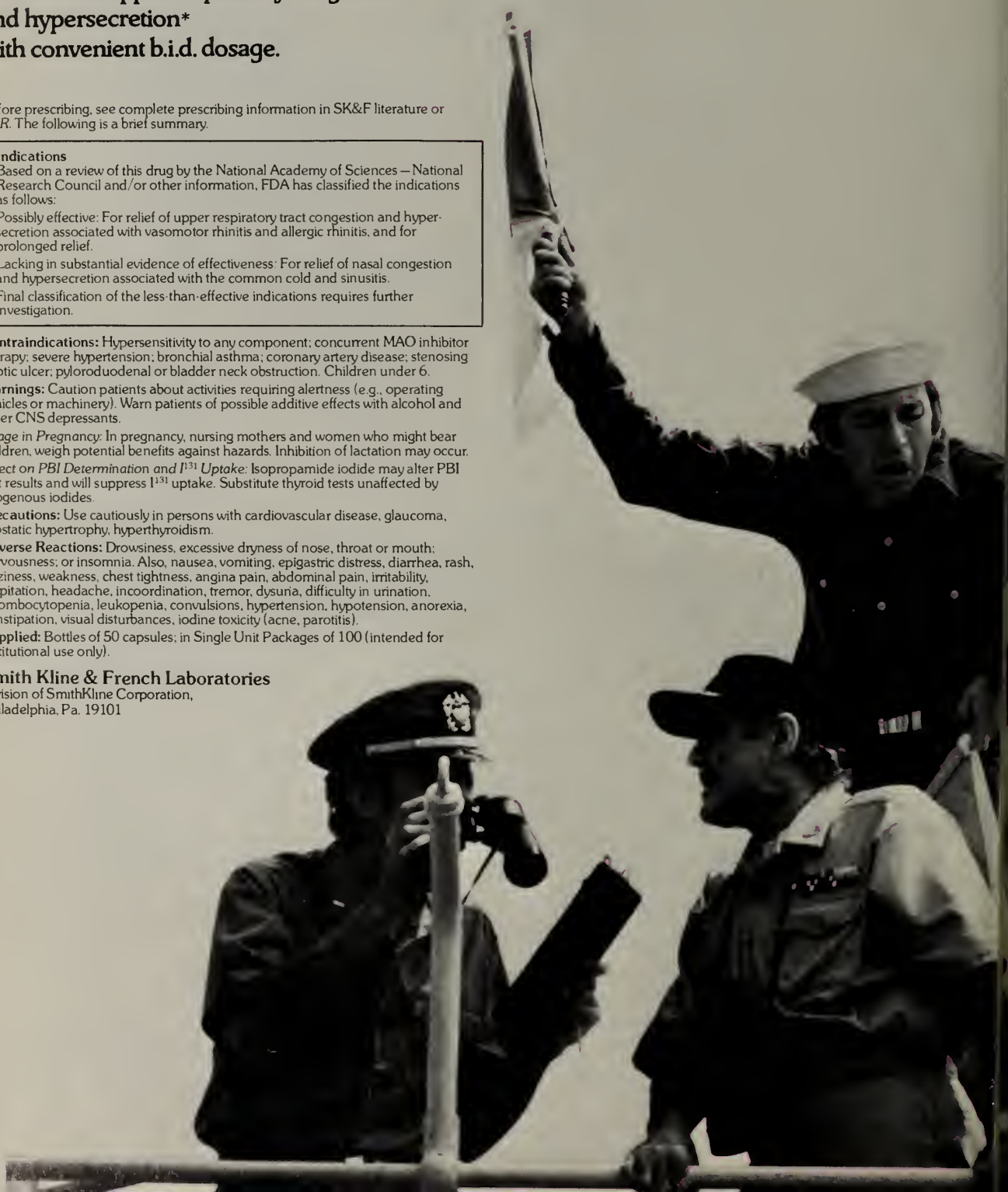
Effect on PBI Determination and I^{131} Uptake: Isopropamide iodide may alter PBI test results and will suppress I^{131} uptake. Substitute thyroid tests unaffected by exogenous iodides.

Precautions: Use cautiously in persons with cardiovascular disease, glaucoma, prostatic hypertrophy, hyperthyroidism.

Adverse Reactions: Drowsiness, excessive dryness of nose, throat or mouth; nervousness; or insomnia. Also, nausea, vomiting, epigastric distress, diarrhea, rash, dizziness, weakness, chest tightness, angina pain, abdominal pain, irritability, palpitation, headache, incoordination, tremor, dysuria, difficulty in urination, thrombocytopenia, leukopenia, convulsions, hypertension, hypotension, anorexia, constipation, visual disturbances, iodine toxicity (acne, parotitis).

Supplied: Bottles of 50 capsules; in Single Unit Packages of 100 (intended for institutional use only).

Smith Kline & French Laboratories
Division of SmithKline Corporation,
Philadelphia, Pa. 19101



How many of your patients know what vitamin A and vitamin C are?

But they do know what vegetables and fruits are.

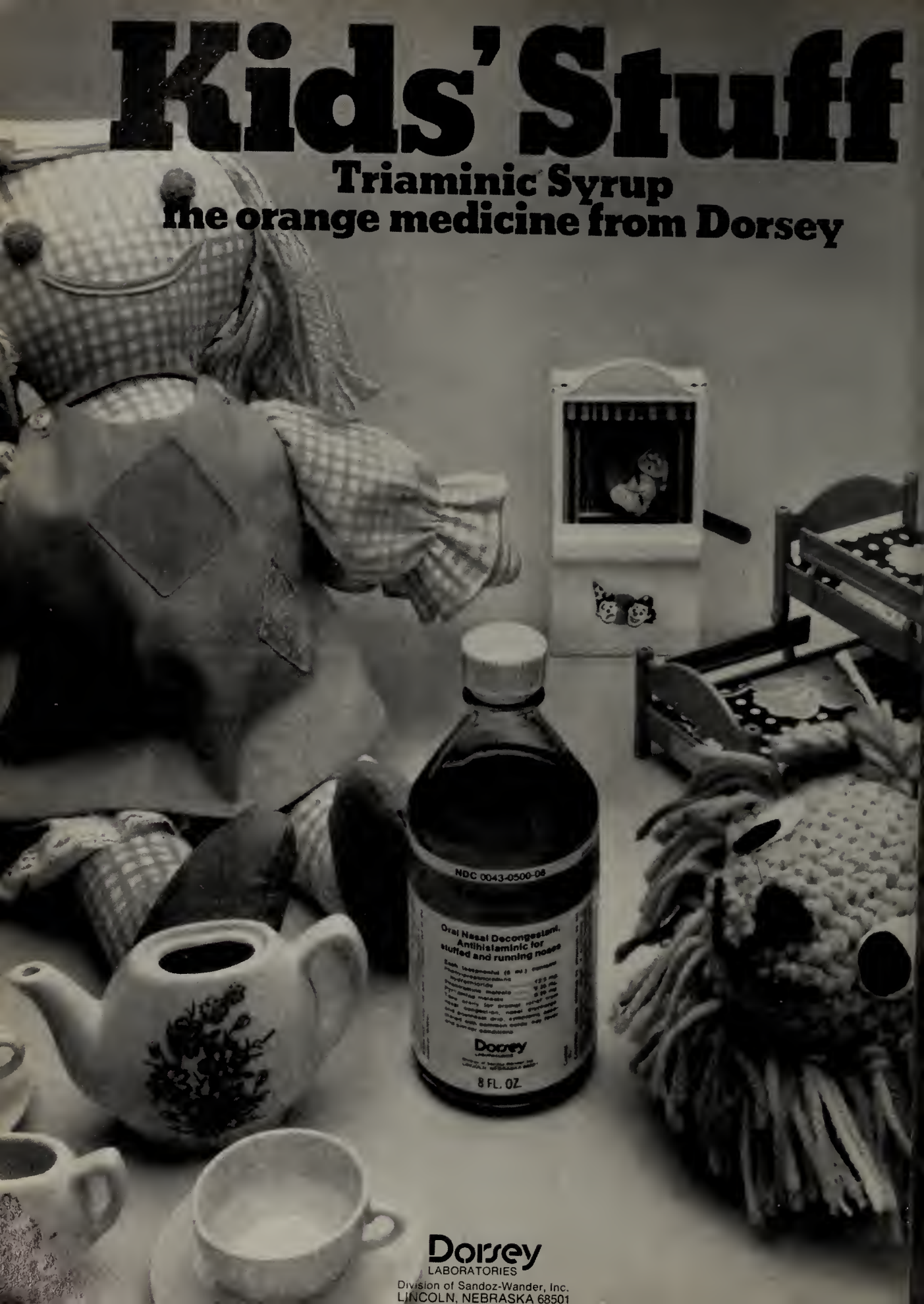
The foods above have several nutrients in common. The principal ones are vitamins A and C, important for building body resistance to infection. Because citrus fruits, leafy greens, broccoli, carrots, cabbage and others provide these nutrients, these kinds of foods are classified as the Vegetable & Fruit Group in the U.S. Department of Agriculture's Four Food Groups system.

Some physicians counsel patients in terms of nutrients. Which is easier for them to understand—foods or nutrients?

For attractive, color copies of the Four Food Groups guide for your patients, write: Dairy Council of California, Box 28F, Sacramento, CA 95825.

Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.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Triaminic Syrup
the orange medicine from Dorsey
NDC 0043-0500-08
Oral Nasal Decongestant, Antihistaminic for stuffed and running noses
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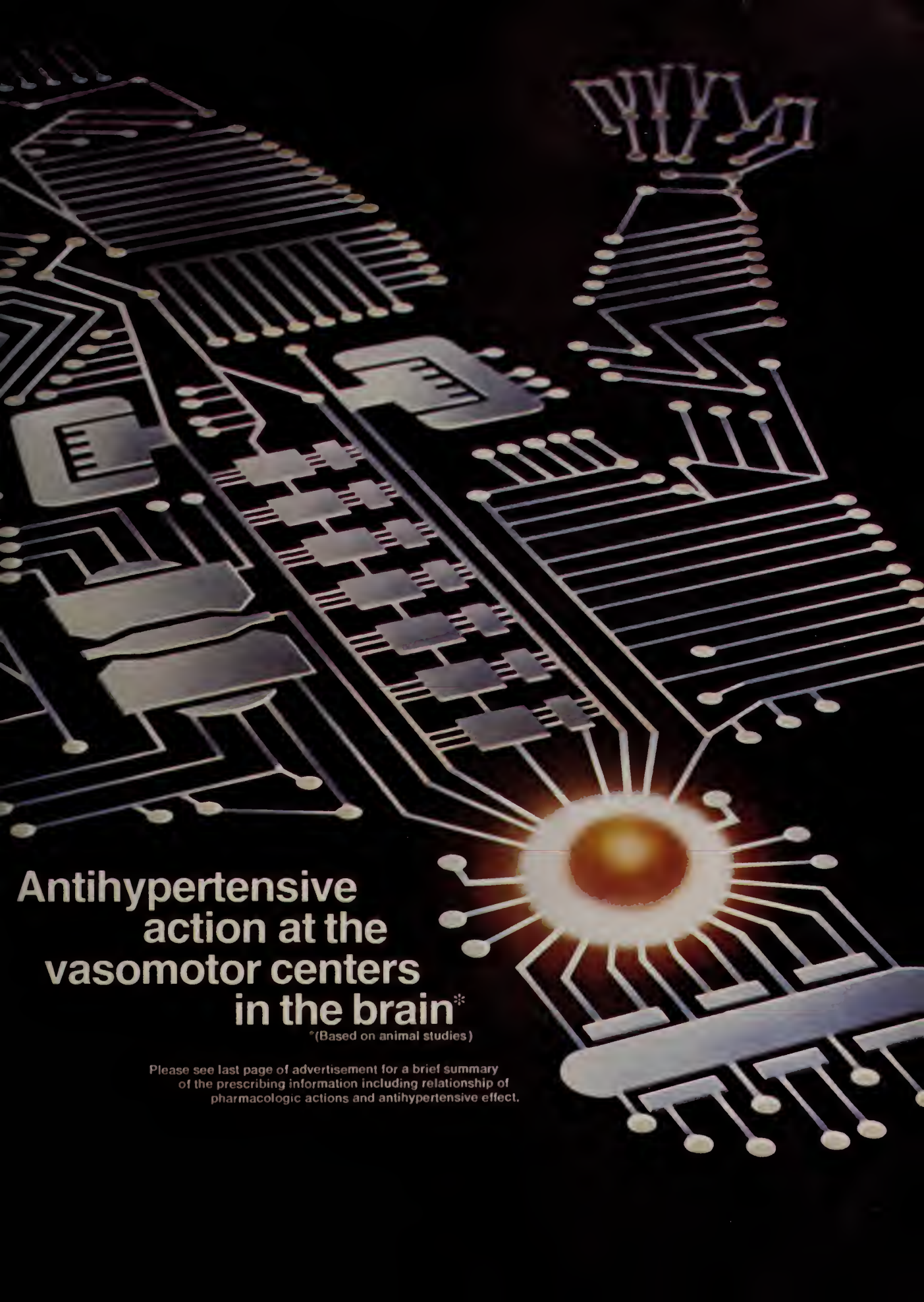
Antihypertensive action at the vasomotor centers in the brain*
*(Based on animal studies)
Please see last page of advertisement for a brief summary of the prescribing information including relationship of pharmacologic actions and antihypertensive effect.

Now... antihypertensive action at the vasomotor centers in the brain

new Catapres®

Tablets of 0.1 and 0.2 mg

(clonidine hydrochloride)

Effective in hypertension, mild to severe

- Mild and infrequent orthostatic hypotension
- Normal hemodynamic responses to exercise are unaffected
- Renal blood flow and glomerular filtration rate essentially unchanged
- Mild to moderate potency

Central action:

Catapres appears to lower blood pressure through central alpha-adrenergic stimulation, as shown in animal studies. This results in diminution—but not blocking—of sympathetic outflow from cardiac accelerator and vasoconstrictor centers in the medulla.

- Not a "depleter"
- Not a "blocker"
- Not an "inhibitor"
- Not a "false transmitter"

pres Man
ne hydrochloride)
s new pathways
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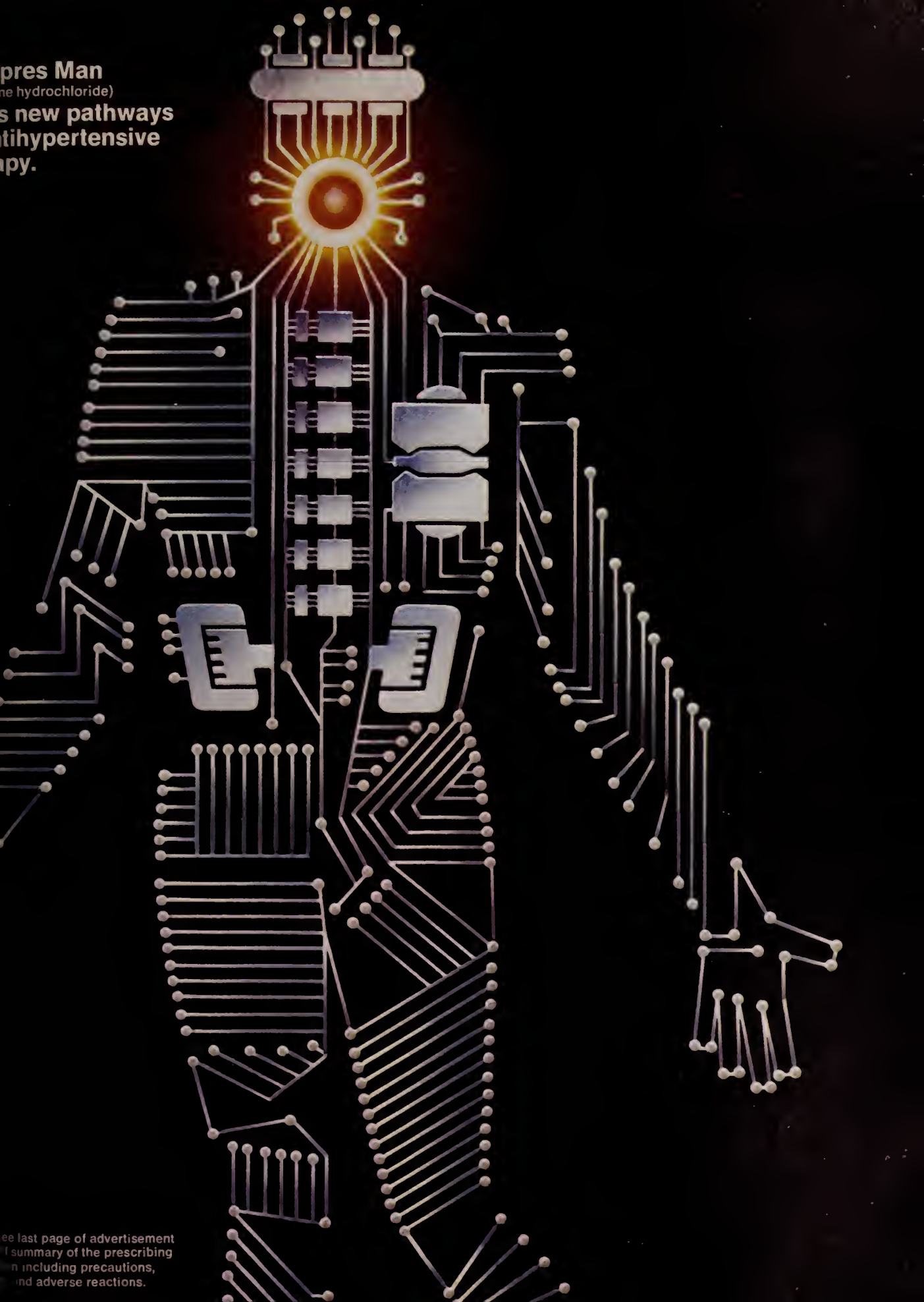
apy.



ee last page of advertisement
f summary of the prescribing
n including precautions,
nd adverse reactions.

new Catapres
(clonidine hydrochloride)

Effective in hypertension, mild to severe

Catapres is distinguished by its broad clinical usefulne in the treatment of hypertension.

More than 600 major published papers*

The extensive experimental and clinical work with Catap s has been reported in hundreds of papers published in scientific journals in this country and abroad. Controlle studies[1-7] plus numerous other clinical evaluations have demonstrated that Catapres is an effective antihypertensive drug with these desirable properties:

---

does not alter normal hemodynamic responses to exerc e

---

renal blood flow and glomerular filtration rate essentia unchanged

---

antihypertensive response enhanced by diuretics such as chlorthalidone

---

compatible with other antihypertensive agents

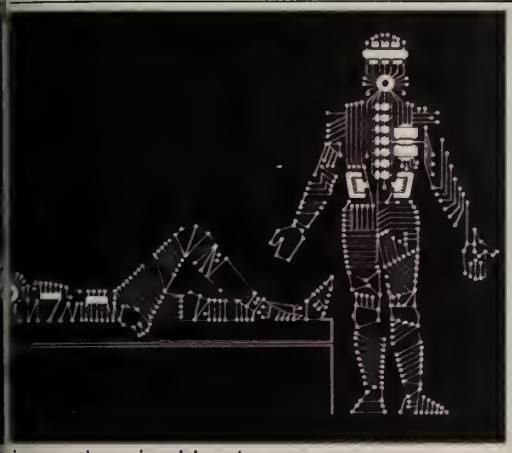
---

has been shown to reduce plasma renin activity and to decrease excretion of aldosterone and catecholamines
(See ACTIONS section of Brief Summary)

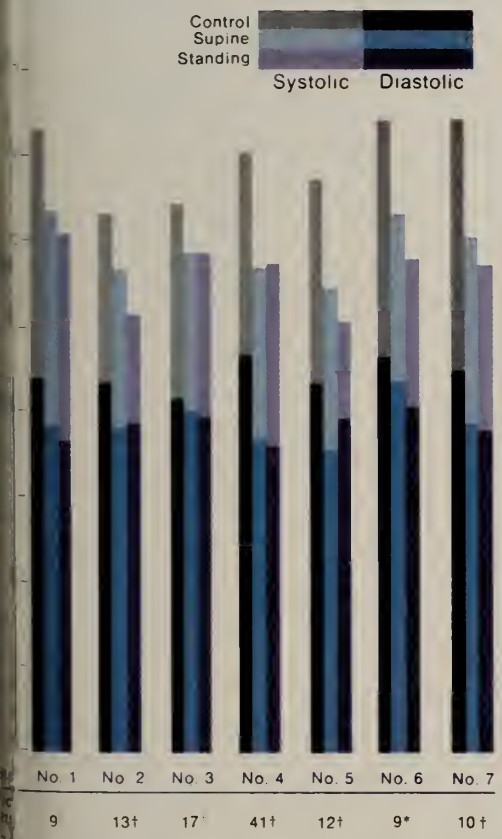
What to watch for—The principal side effects of Catapres are d mouth, sedation, and drowsiness. Constipation, dizziness, headac e, and fatigue also have been reported. Generally, these effects tend t diminish with continued therapy. As with other antihypertensive age s, tolerance may develop in some instances. For a more detailed disc - sion of side effects, warnings, and precautions, see the brief sumr ry of prescribing information on the last page of this advertisement consult the Catapres package insert.

*Complete Catapres bibliography available on request.

) and infrequent
ostatic effects

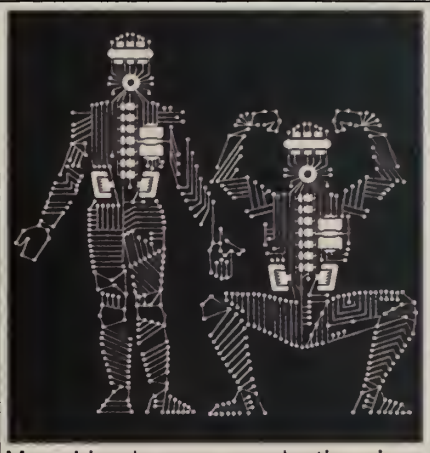


ing and supine blood pressure
nse at the conclusion of therapy in
trolled studies[1-7]

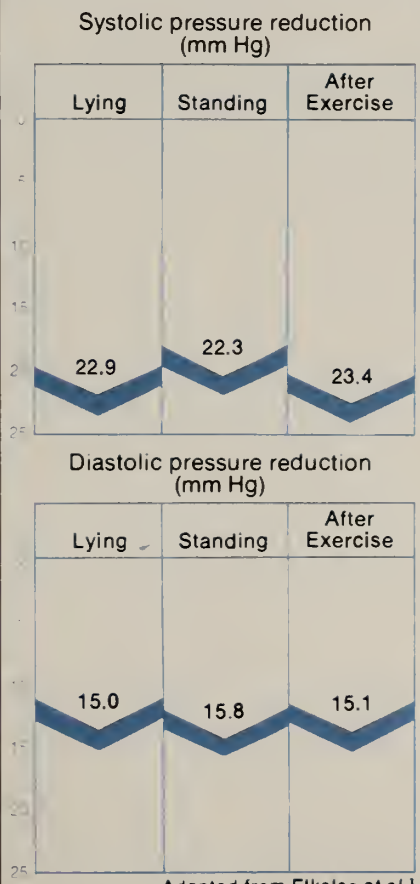


ived Catapres alone.
ved Catapres + a diuretic.
In study No.4, blood pressure was taken in the
g rather than the supine position.

Normal hemodynamic responses to exercise not altered

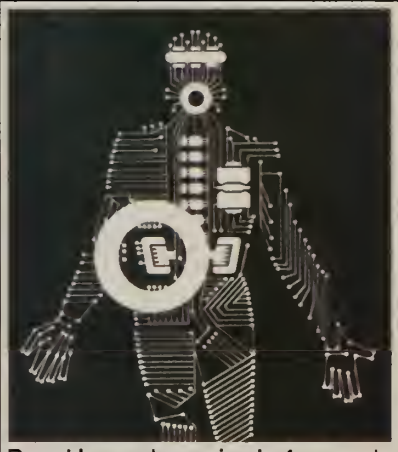


Mean blood pressure reductions in 9 hypertensive patients receiving Catapres (0.15 mg daily) for 4 weeks

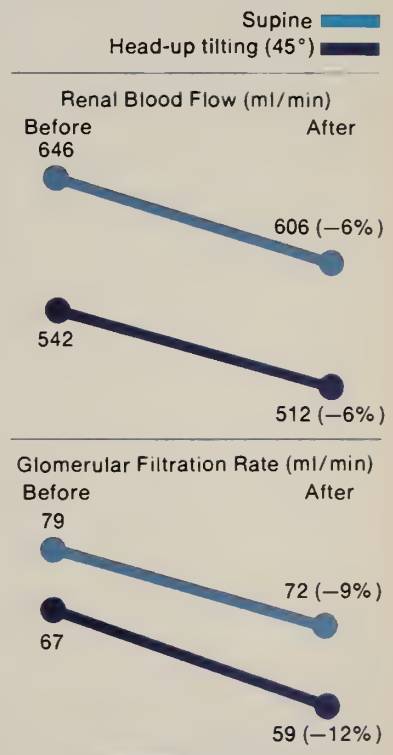


Adapted from Elkeles *et al.*[1]

Renal blood flow and glomerular filtration rate essentially unchanged

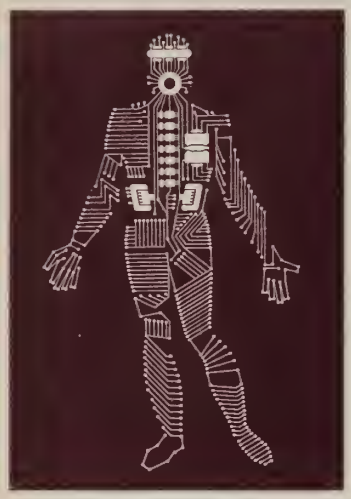


Renal hemodynamics before and after Catapres in 7 hypertensive patients. Mean blood pressure reductions were significant in both the supine position (from 155 to 128 mm Hg) and the standing position (from 151 to 101 mm Hg).



Adapted from Onesti *et al.*[8]

New from Boehringer Ingelheim



new Catapres®
(clonidine hydrochloride)

It's easy to start with Catapres. The usual starting dose of Catapres is one 0.1 mg tablet twice daily. Increments of 0.1 to 0.2 mg per day (up to the maximum daily dose of 2.4 mg) may be made until the desired blood pressure response is achieved.

How to stop Catapres. Reduce the dose gradually over two to four days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients on Catapres should be instructed not to discontinue therapy without consulting their physician. It has been demonstrated that a rapid rise in blood pressure, should it occur, can be reversed by resumption of Catapres or by administration of intravenous phentolamine.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Actions: The mechanism of action appears to be central alpha-adrenergic stimulation as demonstrated in animal studies. This results in inhibition of bulbar sympathetic cardioaccelerator and sympathetic vasoconstrictor centers, thereby decreasing sympathetic outflow from the brain. Other studies in humans have provided evidence of a reduction in plasma renin activity and the excretion of aldosterone and catecholamines. The exact relationship between these pharmacologic actions of Catapres (clonidine hydrochloride) in humans and its antihypertensive effect has not been fully elucidated at this time.

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in poter tially hazardous activities, such as operating macl or driving, should be advised of the sedative effec This drug may enhance the CNS-depressive effec alcohol, barbiturates and other sedatives. Like any agent lowering blood pressure, clonidine hydroch should be used with caution in patients with seve coronary insufficiency, recent myocardial infarcti cerebrovascular disease or chronic renal failure.
As an integral part of their overall long-term ca patients treated with Catapres (clonidine hydroch should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-rela abnormal ophthalmologic findings have been rec with Catapres (clonidine hydrochloride), in severa studies the drug produced a dose-dependent incr in the incidence and severity of spontaneously oc ring retinal degeneration In albino rats treated fo 6 months or longer.

Adverse Reactions: The most common reactions dry mouth, drowsiness and sedation. Constipatio dizziness, headache, and fatigue have been repo Generally these effects tend to diminish with con therapy. The following reactions have been assoc with the drug, some of them rarely. (In some inst an exact causal relationship has not been establi These include: Anorexia, malaise, nausea, vomiti parotid pain, mild transient abnormalities in liver tion tests; one report of possible drug-induced h titis without icterus and hyperbilirubinemia in a p receiving clonidine hydrochloride, chlorthalidone papaverine hydrochloride. Weight gain, transient tion of blood glucose, or serum creatine phosphol congestive heart failure, Raynaud's phenomenon dreams or nightmares, insomnia, other behaviora changes, nervousness, restlessness, anxiety and depression. Also rash, angioneurotic edema, hive urticaria, thinning of the hair, pruritus not associ with a rash, impotence, urinary retention, increas sensitivity to alcohol, dryness, itching or burning eyes, dryness of the nasal mucosa, pallor, gynec mastia, weakly positive Coombs' test, asymptoma electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, s lence, diminished or absent reflexes and vomitin lowed the accidental ingestion of Catapres (clon hydrochloride) by several children from 19 month 5 years of age. Gastric lavage and administratio analeptic and vasopressor led to complete recov within 24 hours. Tolazoline in intravenous doses 10 mg at 30-minute intervals usually abolishes a fects of Catapres (clonidine hydrochloride) overd

How Supplied: Catapres, brand of clonidine hydr chloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of
For complete details, please see full prescribi information.
Under license from Boehringer Ingelheim Gmb

References: 1. Elkeles, R. S., Goldby, F. S. and D. O.: A Double Blind Study of Catapres, A New tensive Agent, *in* Conolly, M. E. (ed.): Catapres i Hypertension, London, Butterworths, 1970, pp. 1 2.Freis, E. D.: Data on file at Boehringer Ingelhe 3. Hickler, R. B.: Data on file at Boehringer Inge Ltd. 4. Mroczek, W. J., Leibel, B. A. and Finnerty Jr.: Comparison of clonidine and methyldopa in tensive patients receiving a diuretic, Am. J. Card **29**:712, 1972. 5. Putzeys, M. R. and Hoobler, S. V Comparison of clonidine and methyldopa on bloo sure and side effects in hypertensive patients, A Heart J. **83**:464, 1972. 6. MacDonald, R. H. and S A.: Data on file at Boehringer Ingelheim Ltd. 7. dall, W. M., Toubes, D. B. *et al.*: Hypertensive e clonidine and chlorthalidone, Am. Heart J. **82**:31 8. Onesti, G. *et al.*: Pharmacodynamic effects of antihypertensive drug, Catapres (ST-155), Circul **39**:219, 1969.

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Boehringer Ingelheim

Boehringer Ingelheim Ltd.
Elmsford, New York 10523

Who suffers more

when mother's child suffers from colic, diarrhea or similar malady?

Soyalac and new I-Soyalac can be an effective answer.

›yalac from isolated
›tein without corn.

I-Soyalac and regular Soyalac is palatable, readily digestible and assimilated. It simulates human milk in appearance, taste and texture. It is complete with vitamins and minerals. It is suitable for infants and children who are sensitive to or cannot tolerate cow's milk.

For nearly a quarter of a century, Soyalac has proven its value—in promoting growth and development—as proven by extensive clinical data.

Available in four forms: • I-Soyalac Concentrated • Soyalac Concentrated • Soyalac Ready-to-Serve • Soyalac Powder.

send to: Loma Linda Foods
Medical Products Division
Riverside, Calif. 92505

Please send me free sample and literature.

Name _____

Address _____

City _____ State _____ Zip _____

Or a simple note on your prescription form will do.

WJM—11

a NEW effective non-phenothiazine for post-op EMETIC-CONtrol

Unsurpassed efficacy

Control of emesis has been shown to be equivalent to that achieved with Compazine® (prochlorperazine) and other potent phenothiazines in well-controlled clinical studies.*

Well tolerated

The parenteral solution is non-irritating and does not produce pain at the site of injection. Drowsiness appears to be the most common adverse reaction. Other more significant reactions have been reported: Please refer to the package insert.

Characteristically nonhypotensive

Emete-con™ (benzquinamide HC
be used in marginally hypotensive pa
since it does not characteristically cau
potentiate hypotension.

No respiratory depress

Emete-con does not characteristi
cause respiratory depression or pote
CNS depressants.

IEF SUMMARY OF PRESCRIBING INFORMATION

tions. Benzquinamide HCl has exhibited antiemetic, antihistaminic, d anticholinergic and sedative action in animals. Studies conducted in s and human volunteers have demonstrated suppression of morphine-induced vomiting; however, relevance to clinical efficacy not been established. The mechanism of action in humans is nown. Onset of antiemetic activity in humans usually occurs within ninutes.

Benzquinamide metabolism has been studied in animals and in man. both species, 5-10% of an administered dose is excreted unchanged he urine. The remaining drug undergoes metabolic transformation in liver by at least three pathways to a spectrum of metabolites which excreted in the urine and in the bile, from which the more polar abolites are not reabsorbed but are excreted in the feces. The half-in plasma of Emete-con is about 40 minutes. More than 95% of an unistered dose was excreted within 72 hours in animal studies using -labeled benzquinamide. In blood, benzquinamide is about 58% nd to plasma protein.

cations. Prevention and treatment of nausea and vomiting ciated with anesthesia and surgery.

he prophylactic use should be restricted to those patients in whom sis would endanger the results of surgery or result in harm e patient.

ntraindications. Contraindicated in individuals who have onstrated hypersensitivity to the drug.

rnings. *Use in Pregnancy:* No teratogenic effects of benzquinamide e demonstrated in reproduction studies in chick embryos, mice, rats rabbits. The relevance of these data to the human is not known. wever, safe use of this drug in pregnancy has not been established its use in pregnancy is not recommended.

Use in Children: As the data available at present are insufficient to blish proper dosage in children, use in children is not recommended.

Intravenous use: Sudden increase in blood pressure and transient ythmias (premature ventricular and auricular contractions) have n reported following intravenous administration of benzquinamide. l a more predictable pattern of the effect of intravenous quinamide has been established, the intramuscular route of tration is considered preferable. The intravenous route should ricted to patients without cardiovascular disease and receiving no esthetic cardiovascular and/or concomitant cardiovascular drugs.

tions. Benzquinamide, like other antiemetics, may mask signs e dosage of toxic drugs or may obscure diagnosis of such conditions inal obstruction and brain tumor.

erse Reactions. Drowsiness appears to be the most common . One case of pronounced allergic reaction has been ered, characterized by pyrexia and urticaria.

ystem Affected– *Autonomic Nervous System:* Dry mouth, ring, sweating, hiccoughs, flushing, salivation, blurred vision.

ovascular System: Hypertension, hypotension, dizziness, atrial on, premature auricular and ventricular contractions.

ral Nervous System: Drowsiness, insomnia, restlessness, , excitement, nervousness.

rointestinal System: Anorexia, nausea.

culoskeletal System: Twitching, shaking tremors, weakness.

: Hives, rash.

Systems: Fatigue, chills, increased temperature.

Dosage and Administration. *Intramuscular:* 50 mg (0.5 mg/kg-1.0 mg/kg)

First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-con should be injected well within the mass of a larger muscle. The deltoid area should be used only if well developed. Injections should not be made into the lower and mid-thirds of the upper arm. Aspiration of the syringe should be carried out to avoid inadvertent intravascular injection.

Therapeutic blood levels and demonstrable antiemetic activity appear within fifteen minutes of intramuscular administration. When the objective of therapy is the prevention of nausea and vomiting, intramuscular administration is recommended at least fifteen minutes prior to emergence from anesthesia.

Intravenous: 25 mg (0.2 mg/kg-0.4 mg/kg as a single dose) administered slowly (1 ml per 0.5 to 1 minute). Subsequent doses should be given intramuscularly.

The intravenous route of administration should be restricted to patients without cardiovascular disease (See WARNINGS). If it is necessary to use Emete-con intravenously in elderly or debilitated patients, benzquinamide should be administered cautiously and the lower dose range is recommended. This preparation must be initially reconstituted with 2.2 ml of sterile water. This procedure yields 2 ml of a solution equivalent to 25 mg benzquinamide/ml, which maintains its potency for 14 days at room temperature. DO NOT REFRIGERATE.

Overdosage. *Manifestations:* On the basis of acute animal toxicology studies, gross Emete-con overdosage in humans might be expected to manifest itself as a combination of Central Nervous System stimulant and depressant effects. This speculation is derived from experimental studies in which intravenous doses of benzquinamide, at least 150 times the human therapeutic dose, were administered to dogs.

Treatment: There is no specific antidote for Emete-con overdosage. General supportive measures should be instituted, as indicated. Atropine may be helpful. Although there has been no direct experience with dialysis, it is not likely to be of value, since benzquinamide is extensively bound to plasma protein.

How Supplied. Emete-con for IM/IV use is available in a vial containing benzquinamide HCl equivalent to 50 mg of benzquinamide in packages of 10 vials.

***Bibliography**

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ROERIG Pfizer

A division of Pfizer Pharmaceuticals
New York, New York 10017

Emete-con™

benzquinamide HCl) IM/IV

ost-op EMETIC-CONtrol

ual adult dose: IM-50 mg., IV-25 mg.

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MediManager is the most complete professional service package ever offered to physicians and dentists. It's designed to be of help in (1) patient billing and collection, (2) patient credit, (3) equipment financing, (4) acquisition of facilities, and (5) estate management.

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"Gentlemen, ongratulations are in order."

"A.H. Robins asked me mpare the banana flavor of their iagel® -PG with the real thing and, ve, I couldn't tell the difference. ven in sip-by-sip comparison. zing!

"There's no unpleasant goric taste because there's no goric. Clever, wouldn't you say? ad, A. H. Robins uses the thera- c equivalent, powdered opium, omote the production of formed stools and lessen the urge. And Donnagel-PG also provides the demulcent-detoxicant effects of kaolin and pectin, plus the antispasmodic benefits of belladonna alkaloids.

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Donnagel with paregoric equivalent

Each 30 cc. contains:

Kaolin	6.0 g
Pectin	142.8 mg
Hyoscyamine sulfate	0.1037 mg
Atropine sulfate	0.0194 mg
Hyoscine hydrobromide	0.0065 mg
Powdered opium, USP	24.0 mg
(equivalent to paregoric 6 ml.) (warning may be habit forming)	
Sodium benzoate (preservative)	60.0 mg
Alcohol, 5%	

℞ Available on oral prescription or without prescription in compliance with applicable state and local law

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Robitussin
Robitussin-DM
Robitussin-PE
Cough Calmer

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OF COLDS,
FLU, AND U.R.I.:
CLEAR
THE
TRACT
WITH THE
ROBITUSSIN®
LINE

Fall and winter coughs are back. Time to help clear the lower respiratory tract with the five Robitussins and Cough Calmers. All contain glyceryl guaiacolate, the efficient expectorant that works systemically to help increase the output of lower respiratory tract fluid. The enhanced flow of less viscid secretions soothes the tracheobronchial mucosa, promotes ciliary action, and makes thick, inspissated mucus less viscid and easier to raise. Available on your prescription or recommendation.

For unproductive coughs

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Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
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Glyceryl guaiacolate ..... 100 mg.
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(warning: may be habit forming)
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Non-narcotic for 6-8 hr. cough control

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Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Dextromethorphan hydrobromide ..... 15 mg.
Alcohol, 1.4%

Robitussin-DM in solid form for "coughs on the go"

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Each Cough Calmer contains:
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Dextromethorphan hydrobromide ..... 7.5 mg.

Clears nasal and sinus passages as it relieves coughs

ROBITUSSIN-PE®

Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Phenylephrine hydrochloride ..... 10 mg.
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MEET THE NEWEST MEMBER OF THE LINE

Comprehensive decongestant action helps control cough and clear stuffy nose and sinuses. Non-narcotic.

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Select the Robitussin® formulation that treats your patient's individual coughing needs:	Expectorant-Demulcent	Cough Suppressant	Long-Acting (6-8 hours)	Nasal, Sinus Decongestant	Non-Narcotic
ROBITUSSIN®	●				●
ROBITUSSIN A-C®	●	●			
ROBITUSSIN-DM®	●	●	●		●
ROBITUSSIN-PE®	●			●	●
ROBITUSSIN®-CF	●	●		●	●
COUGH CALMERS®	■	■	■		■

A. H. Robins Company, Richmond, Va. 23220

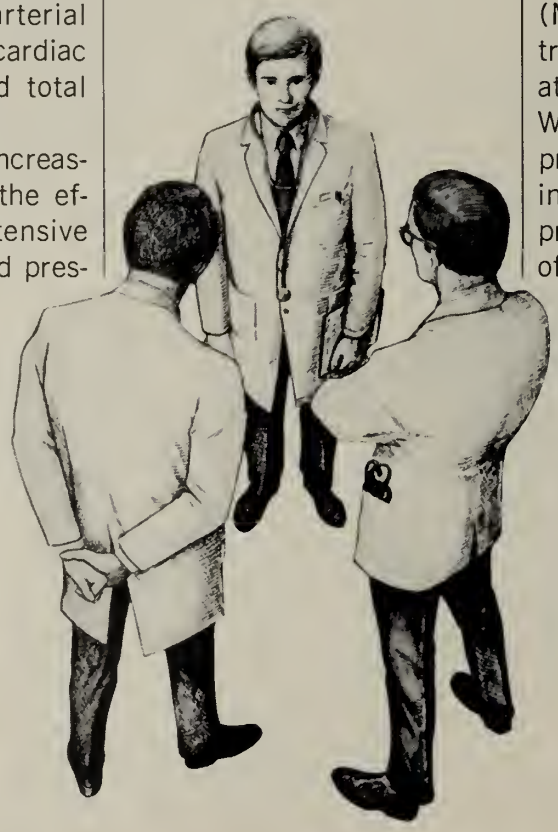
The more physicians consider the hemodynamics of lowering blood pressure...

Most physicians now agree on the importance of reducing blood pressure in the hypertensive patient. But high blood pressure exists, of course, only as part of a complete clinical picture. The hemodynamic profile of well-established essential hypertension is characterized by elevated arterial blood pressure, normal cardiac output, and increased total peripheral resistance.

And so, physicians are increasingly concerned with the effects of an antihypertensive agent not only on blood pressure itself but also on the hemodynamic pattern—in short, with the total effect of the drug. *Does* it indeed help lower blood pressure effectively? *Is* peripheral resistance reduced? *Are* cardiac output and renal functions maintained? And, also, is there likely to be drug-induced postural hypotension serious enough to pose a threat to the patient's cerebrovascular status?

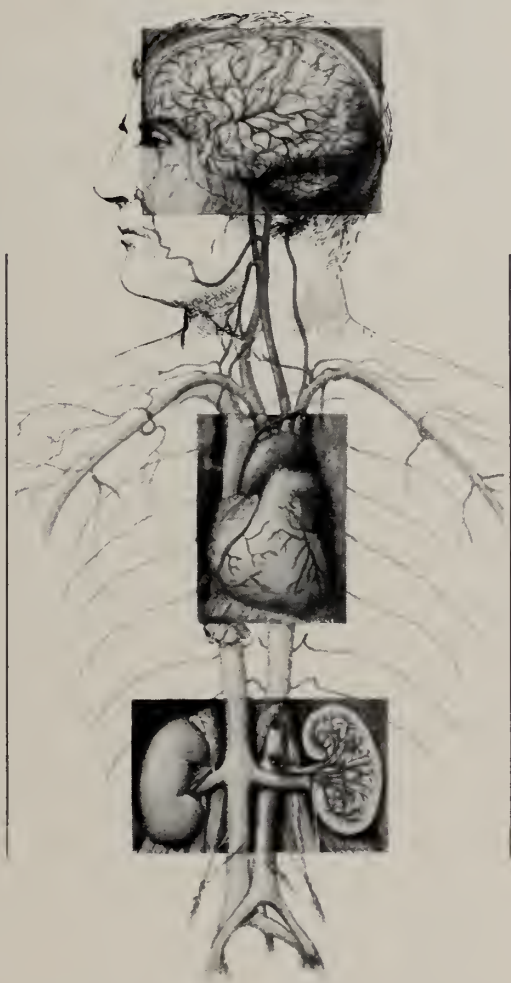
With this emphasis on overall drug performance has come a growing reliance on ALDOMET® (Methyldopa, MSD) in the treatment of sustained moderate hypertension.

With its unique hemodynamic profile, ALDOMET has drawn increasing attention and approval from physicians. First, of course, for its efficacy in



the more physicians rely on this unique antihypertensive

wering blood pressure. But ıere are other considerations ; well. Cardiac output is usu- lymaintained with no cardiac :celeration; in some patients ıe heart rate is actually owed. Peripheral resistance apparently reduced. _DOMET does not usually ›mpromise existing renal nction; it generally does not duce renal blood flow, glo- erular filtration rate, or fil- ıtion fraction. And ALDOMET ;ually does not cause sympto- atic postural or exercise l potension.



Contraindications include active hepatic disease and known sensitivity to the drug. Use with caution in patients with a history of liver disease or dysfunction. Not recommended in pheochromocytoma or pregnancy.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

In most cases of sustained moderate hypertension

TABLETS, 250 mg and 500 mg

ALDOMET®

(METHYLDOPA | MSD)

smoothly lowers blood pressure

NEW now available in 500 mg TABLETS as well as the standard 250-mg tablets

r a brief summary of prescribing information, ıase see following page.

In most cases of sustained moderate hypertension

ALDOMET®
(METHYLDOPA MSD)

smoothly lowers blood pressure

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis. Known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between six and twelve months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at six and twelve months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first six to twelve weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur.

Use in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Methyldopa may interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has occurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure are occasionally seen and include dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency. Angina pectoris may be aggravated. Symptoms of orthostatic hypotension may occur; if symptoms occur, reduction of dosage is suggested. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distention, constipation, flatus, and diarrhea occur occasionally; these generally can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently and are relieved by administering a thiazide diuretic; if edema progresses or signs of pulmonary congestion appear, discontinue drug. A rise in BUN has been observed. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, Bell's palsy, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Note: Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Maximal recommended daily dose is 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

How Supplied: Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

addendu

"Required Reading" For Your Hypertensive Patients

Because of the importance of patient motivation, Merck Sharp & Dohme offers "High Blood Pressure," a concise, pocket-sized booklet that defines the patient's own role in the management of hypertension. This booklet is available for you to give to your patients. It is designed to reinforce your explanation of hypertension and it emphasizes the importance of patient understanding in adhering to the regimen you prescribe.

Please ask your Merck Sharp & Dohme Professional Representative or write Professional Service Department, West Point, Pa. 19486 for a supply of this booklet.

Case history #5

Wayne's well-being comes first.

Wayne's being well comes first.

For two weeks in 1972, Wayne Patton lay unconscious in an Oxnard hospital. Wayne, a deputy sheriff for Ventura County, sustained serious injuries when his patrol car crashed on the way to a robbery scene. The accident left him partially paralyzed and caused disruptions in his ability to see, speak, and walk.

As soon as Wayne was sufficiently recovered, State Fund arranged for his transfer to the Santa Barbara County Rehabilitation Center, where he was given extensive rehabilitation therapy. He made rapid progress toward recovery.

After three months of care, Wayne left the hospital. He was ready to rebuild his life, and State Fund was ready to help. After arranging for continued physical therapy and outpatient medical care, the State Fund staff enrolled him in Work, Inc., a sheltered workshop in Santa Barbara, and also arranged for his friends at the Sheriff's Department to drive him to and from the workshop. In his first week at the shop, Wayne threw away his cane.

Although he was unable to take his old job back, State Fund worked hard to find him a position in a related field. Today, Wayne Patton works full-time as an Air Pollution Control Monitor.

It took a lot of hard work and courage for Wayne to rebuild his life. Most of the credit belongs to him, but a lot of people helped: his wife, his doctors, his friends at the Sheriff's Department, and the people at State Fund.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND

EFFECTIVE APPETITE DEPRESSANT with predictable pharmacological action

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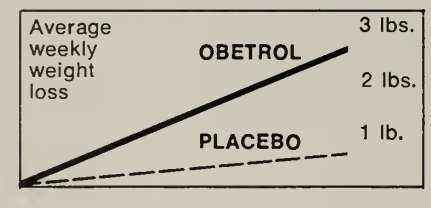
Single entity amphetamine product. Each OBETROL-10 (10 mg. tablet) contains: dextroamphetamine saccharate 2.5 mg., amphetamine aspartate 2.5 mg., dextroamphetamine sulfate 2.5 mg., amphetamine sulfate 2.5 mg. OBETROL-20 (20 mg. tablets) contain twice this potency.

Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

CONTROLLED STUDY —
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant t diarrhea, other gastrointestinal disturbances. Anorexia weight loss may occur as undesirable effects when ampl mines are used for other than the anorectic effect. *Alle* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, ampl mines should be administered at the lowest effective do and dosage should be individually adjusted. Late evening n cation should be avoided because of the resulting insomni

1. Narcolepsy: Usual dose 5 to 60 milligrams per da divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams c raised in increments of 2.5 milligrams at weekly intervals optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, onc twice daily, increased in increments of 5 milligrams at w intervals. Only in rare cases will it be necessary to exce total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per da divided doses.

Overdosage: Manifestations of acute overdosage with amp tamines include restlessness, confusion, assaultiveness, ha c nations, panic states. Fatigue and depression usually f ow the central stimulation. Cardiovascular effects include arr th mias, hypertension or hypotension, and circulatory coll se Gastrointestinal symptoms include nausea, vomiting, diar ea, and abdominal cramps. Fatal poisoning usually terminat in convulsions and coma.

Management of acute amphetamine intoxication is la el symptomatic and includes lavage and sedation with a ba tu rate. Experience with hemodialysis or peritoneal dialys is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 table

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITH UT PRESCRIPTION.

January 97

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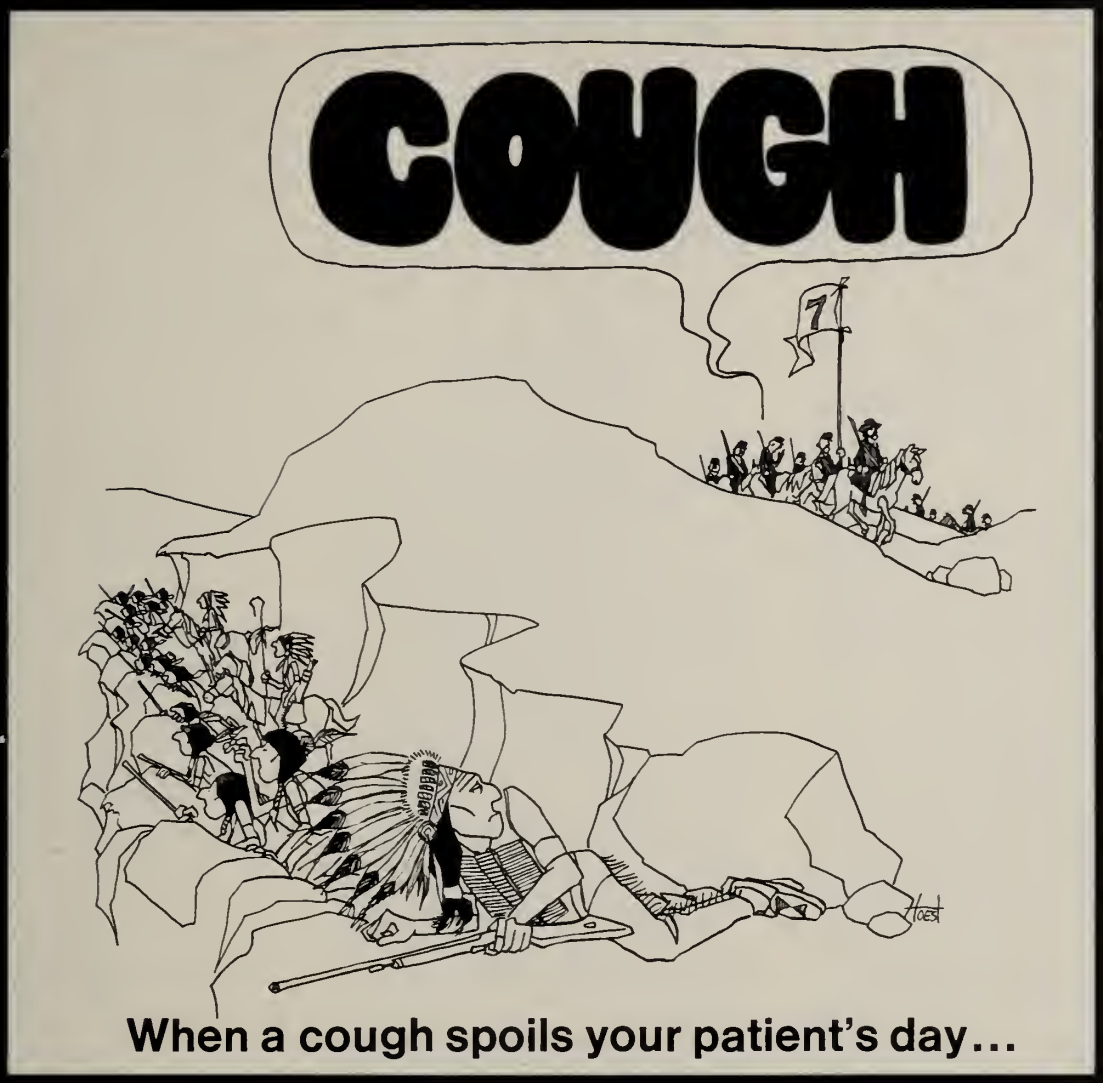

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Each teaspoonful (5 ml.) contains:

Triaminic, 25 mg. (phenylpropanolamine hydrochloride, 12.5 mg.; pheniramine maleate, 6.25 mg.; pyrilamine maleate, 6.25 mg.); glyceryl guaiacolate, 100 mg.; alcohol, 5%.

Available in 8-oz. Family Size and 4-oz.
No Rx needed—recommend over the phone.

The Adult Expectorant that is great for kids, too.

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. . . in every physician's life comes the question, "Where Do I Go from Here?"

We're a 14-year HMO with six clinics, located in coastal towns well south of the city of Los Angeles plus an additional one on the island of Guam. We offer excellent salaries and outstanding benefits including deferred income opportunities and fully vested retirement in ten years. Our planned, continuous growth offers unusual and unique opportunities for the innovative individual.

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GP WANTED: Southern California, Orange County. Three-man clinic long established industrial and private practice, seeking replacement for member rejoining service. Minimal cost, good net, excellent hours. Permanent association desired on expense sharing basis. California license necessary. Open approximately January 1, 1975. Write Box No. 9402, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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PHYSICIAN to direct County Child Health and Disability Prevention Program. Should have at least one year's experience in providing services to children or possess a graduate degree in Public Health. $30,000 per year plus travel. Contact Owen A. Kearns, MD, Kern County Health Officer, P.O. Box 997, Bakersfield, CA 93302; (805) 861-3655.

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Thyroid Nodules and Thyroid Cancer

FRANCIS S. GREENSPAN, MD, *San Francisco*

A review of clinical and laboratory features of thyroid cancer, designed to help in a more precise selection of patients for operation, showed that factors contributing to a high index of suspicion of cancer include previous exposure to low doses of radiation, the presence of a firm, solitary thyroid nodule clearly different from the rest of the gland, a young patient, nodules that are "cold" on scan with radioiodine, and nodules that fail to regress after an adequate trial of thyroxine therapy. Factors contributing to a low index of suspicion of thyroid cancer include soft or cystic lesions, multinodular goiters, nodules that are "hot" on ^{131}I scan, and those that regress during thyroxine treatment.

When these factors are used to select patients for surgical operation, about 30 percent are found to have thyroid cancer.

Until more precise methods for preoperative diagnosis are established, it is suggested that this type of clinical selection may be very helpful in the management of patients with thyroid nodules or nontoxic goiter.

THE THYROID GLAND is unique in that it is easily visible and easily palpable in its location anterior to the trachea. This gland has a tendency to develop nodules, usually benign but occasionally malignant. Although most thyroid cancers are indolent and slow-growing, widespread local metastasis can develop, as well as distant metastasis, resulting in considerable disability and, occasionally, death.[1,2] There have been several excellent reviews on the management of nodular goiter and thyroid cancer.[3-12] Therefore, I intend to review here the clinical differentiation of benign from malignant thyroid nodules.

There has been considerable confusion about the actual prevalence of thyroid cancer. Surgical statistics are particularly unsatisfactory as a source of information. For example, in 1925 at the University of California Medical Center, San Francisco, thyroidectomy was done in approximately 290 patients, and ten cancers were found. This is an incidence of about 3.5 percent. In 1966 thyroidectomy was carried out in 100 patients and 20 cancers were found. This is an incidence of 20

From the Department of Medicine, University of California, San Francisco.

This work was supported in part by research grant C1-4C from the American Cancer Society.

Presented in part at the regional scientific meeting of the American College of Physicians, held in conjunction with the California Medical Association, San Francisco, California, March 2, 1974.

Submitted August 1, 1974.

Reprint requests to: F. S. Greenspan, MD, 125-U, University of California, San Francisco, San Francisco, CA 94143.

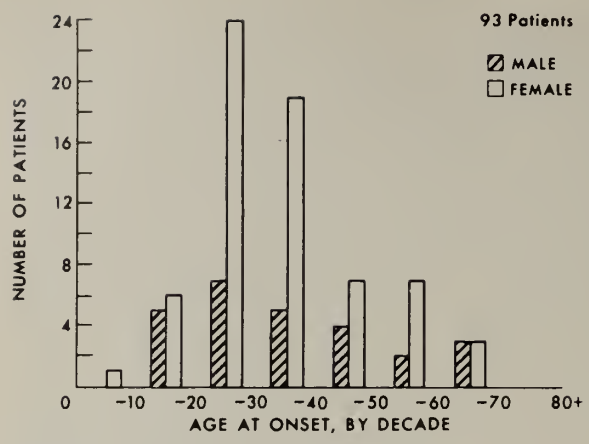

Chart 1.—Distribution by age and sex in a group of 93 patients with proven thyroid cancer.

percent (Goldman L: personal communication). Does this mean that the incidence of cancer has increased? On the contrary, it suggests that the indications for thyroidectomy are changing, and that more of the patients who have thyroid cancer are being selected for operation, whereas fewer who do not have cancer are operated upon.

In the state of Connecticut, all malignant diseases are reported, and excellent statistics are available. Between 1935 and 1970, there has been a gradual increase in the incidence (newly diagnosed cases per year) of thyroid cancer in females, from about 1.5 to 4 per 100,000, and in males, from 0.5 to 1.5 per 100,000.[13,14] Mortality figures from 24 countries, gathered between 1952 and 1963, indicate a drop in deaths from thyroid cancer from about 1.5 per 100,000 in 1952 to 1 per 100,000 in 1963.[15] Interestingly, the death rates in males and females are equal despite the higher incidence of thyroid malignant disease in females. Although the prevalence (total number) of patients with nodular goiter in the United States varies in different geographical locations, Sokal has estimated a minimum prevalence of nodular goiter in the United States at 4 percent, or 4,000 cases per 100,000 population.[4] Mustacchi and Cutler have estimated the incidence of thyroid cancer in the United States as about 0.0025 percent, or 2.5 cases per 100,000.[16] Thus, only a small fraction of patients with nodular goiter will have cancer of the thyroid gland. Although thyroid cancer is an indolent disease and survival is measured in years rather than days or months, it can be a lethal illness.[1,2,17] The question, then, is which nodular lesions are malignant?

TABLE 1.—*Summary of Clinical Characteristics of 93 Patients with Proven Thyroid Cancer*

Sex ratio	Male to female, 1:3
Age at onset	4 to 66 years
History	Recent growth (71%) Lesion present more than one month (65%) Previous radiation therapy (33%) Familial history of thyroid disease (24%)
Physical examination	Firm nodule (92%) Solitary nodule (86%); multinodular (10%) Nodule larger than 2 centimeters in diameter (67%) No palpable nodule (6%) Palpable lymph nodes (33%)
Uptake of ^{131}I	"Cold" (92%; 34 of 37)
Response to therapy	Did not regress after thyroxine therapy (100%; 21 of 21)

Clinical Characteristics of a Group of Patients with Cancer of the Thyroid

I recently reviewed the clinical characteristics of a group of 93 patients with proven thyroid cancer diagnosed during the past ten years. The ratio of male to female patients was about 1 to 3. The age at diagnosis ranged from 4 years to 66 years (Chart 1). There is a peak incidence in the age range of 20 to 40 years in the female group, whereas the number of male patients was relatively constant for each decade. (These data are not adjusted for the percentage of each age group represented in the population.) Age-adjusted data on the incidence of thyroid cancer, presented by Christine et al,[14] showed a peak incidence between the ages of 20 and 40 in female patients, with secondary peaks at age 60 and age 80. We did not see the late peaks in thyroid cancer in our smaller group.

Clinical characteristics of these 93 patients (Table 1) may be summarized as follows:

Although the goiter had been present in most patients for more than a month, 71 percent had evidence of recent growth, either by patient observation or by physician evaluation. In one series,[18] most of the goiters containing cancer had been present more than one year before operation. Thus, recent growth is probably a more significant finding than total duration of the goiter. One-third of the patients had received therapeutic irradiation to the face or neck area. Therapy was administered as early as the first week of life or as late as 30 years of age, and the thyroid cancer was

diagnosed from six to forty years after exposure to radiation. Indications for radiation therapy were reported to have been thymic irradiation for respiratory distress of the newborn, treatment of recurrent tonsillitis or adenoiditis, treatment of cervical lymphadenopathy, or treatment of the face and upper chest for severe acne.

The most striking physical finding indicative of thyroid malignant disease was a large (more than 2 centimeters), firm, solitary nodule, clearly different from the rest of the gland. Cancer in multinodular goiter was rare, and usually involved a "dominant" nodule, which was different from the rest of the gland. A few patients presented with a large, diffuse goiter that was unusually firm; this was the presentation of anaplastic carcinoma or lymphoma. In a few patients, no nodule was palpable at all; either these patients presented with metastatic lesions in lymph nodes as the first symptom of the disease, or the cancer was found as a microscopic focus, as it was, for example, in one patient with Graves' disease. About one-third of this group of patients had palpable lymph nodes at the time of initial examination.

In patients who had radioiodine scans, the nodules were almost all "cold"; in the few that were not clearly "cold," the nodule was too small to delineate on the scan. In 21 patients, thyroxine had been administered in an attempt to reduce the size of the lesion; in none of these patients was this therapy effective.

Most of the patients had papillary carcinoma or mixed papillary and follicular carcinoma (Table 2). The incidence of metastatic lesions, either intraglandular or to regional lymph nodes, was remarkably high.

TABLE 2.—*Pathologic Classification of Thyroid Cancer in a Group of 93 Patients*

Type	*Number*	*Percentage with Metastasis*
Papillary	51	57
Follicular	18	67
Papillary and follicular	17	88
Anaplastic, lymphoma	5	100
Medullary	2	50

Radiation Exposure and Thyroid Cancer

Duffy and Fitzgerald in 1950 reported upon 28 patients less than 18 years old who had cancer of the thyroid gland. Ten of them had received radiation therapy to the neck or chest in infancy.[19] Winship and Rosvoll[20] looked at records of a large group of children under the age of 15 who had had carcinoma of the thyroid gland. Eighty percent of them had received x-ray therapy to the thymus, tonsils, skin, or cervical lymph nodes. A peak incidence of cancer occurred around 1955. Although this epidemic of thyroid cancer has subsided, deGroot and Paloyan recently reported that 20 of 50 adult patients with thyroid cancer had received radiation therapy at some time in the past.[21] Similarly, in our group, 22 of 66 had a history of previous x-ray therapy.

Several types of radiation exposure have been investigated (Table 3). In a retrospective study, Pincus et al reviewed 2,878 patients who had received radiation therapy to the thymic area in infancy.[22] The incidence of nodular goiter was 28 percent, and of thyroid cancer 4 percent. After exposure to radiation fallout in the Marshall Islands in 1954, there was a very high incidence of nodular goiter, particularly in the exposed children, and the incidence of thyroid cancer was again about 4 percent.[23] The incidence of thyroid cancer among the survivors of the Nagasaki-Hiroshima atom bombs was much lower, about 0.4 percent, although it was higher in persons less than 20 years of age at the time of exposure, and in those exposed to 50 or more rads of atomic radiation.[24] On the other hand, after radioiodine therapy for hyperthyroidism, which results in a

TABLE 3.—*Incidence of Thyroid Lesions After Irradiation*

Type of Irradiation	*Estimated Dose to Thyroid*	*Lesion*
Thymic irradiation	335 R	Nodular goiter—28% Carcinoma—4%
Radiation fallout	Gamma, 175 R; beta, 700 to 1400 R	Nodular goiter Children—80% All—27% Carcinoma—4%
Radioiodine therapy	10,000 R	Hypothyroidism—70% Nodular goiter in children—16% Cancer—rare

much higher dose of radiation to the thyroid, the occurrence of hypothyroidism is very high,[25] but the incidence of thyroid cancer is very low, about 0.1 percent.[26] There was, however, a significant incidence of thyroid nodules in patients treated with radioiodine before their twentieth birthday.[27]

Even tiny doses of radiation administered to the scalp of children for treatment of ringworm, where the estimated dose to the thyroid was only 5 to 6 R, was associated with five-fold increase in the incidence of thyroid cancer over that of sibling controls.[28] Larger doses of external radiation, which were used to treat adults with Graves' disease in the early 1940's, were followed in ten to twenty years with malignant lesions in the pharynx in some patients, but cancer of the thyroid was not reported.[29] Similarly, high-dose external radiation for malignant lymphoma was associated with later development of hypothyroidism in many patients, but not with development of thyroid carcinoma.[30]

These data suggest an increasing incidence of nodular goiter and hypothyroidism with increasing doses of radiation therapy, and a decidedly increased susceptibility in children as compared with adults. The risk of thyroid cancer seems to be related to age and to dose in a lower dose range (50 to 500 R). At higher doses, 2,000 R or more, the risk of thyroid cancer is reduced.[31] This may be due to injury to thyroid cells at high radiation doses with failure of the cell to replicate.

Thus, irradiation induces nodular goiters in many patients, and cancers in a few.[32] A history of radiation therapy in a child, or even in an adult, makes one more strongly suspicious of the possibility of cancer.

Major Factors in Clinical Suspicion of Thyroid Cancer

Table 4 summarizes factors to be considered in differential diagnosis. A familial history of goiter usually suggests a benign lesion such as Hashimoto's thyroiditis or dyshormonogenesis. Similarly, residence in an endemic goiter area might be expected to be associated with a high incidence of nontoxic goiter, but not necessarily a high incidence of cancer. The incidence of malignant lesions in older women is relatively low. Cancer is not usually found in diffuse or multinodular goiters. Soft nodules are usually not malignant. In contrast to this, a nodule in a child, a young adult, or a male patient of any age would have a higher index of suspicion of malignant change. The most common presenting malignant thyroid lesion is a solitary, firm, or dominant nodule in the thyroid gland. The presence of vocal cord paralysis, hoarseness, palpable lymph nodes, or distant metastatic lesions would certainly be highly suggestive of malignant disease of the thyroid gland. A high antithyroid antibody titer would be more suggestive of Hashimoto's thyroiditis than of malignant disease.

Scanning Techniques in Evaluation of Nodules

Measurement of the uptake of radioiodine by scanning has been very helpful in the differential diagnosis of thyroid nodules. A nodule that picks up more radioiodine than surrounding tissue—a "hot" nodule—is rarely malignant, whereas malignant lesions occur in 5 to 20 percent of patients with "cold" nodules. Displacement of normal thyroid tissue suggests fixation of the nodule, and this is frequently found in large neoplastic lesions. It is important that the nodule be carefully marked under the scanner to clarify its position in relationship to the scan.[33-36]

Newer scanning techniques have become very useful in differential diagnosis. The vascular flow pattern of thyroid nodules has been evaluated with [^{99m}]TcO_4. Nodules that have a nonvascular flow pattern are almost never malignant, whereas malignant lesions are associated with an early blood flow pattern of the vascular type.[37] Other scanning agents, such as [^{75}Se]methionine, ^{131}cesium, ^{67}gallium citrate, and [^{99m}Tc]bleomycin, have also been investigated. These agents are taken up by malignant lesions, but are also frequently taken up in significant amounts by benign lesions; therefore, they have not proved as useful for differentiating benign from malignant lesions as had been hoped.[38-41]

The echo scan has been particularly helpful in the diagnosis of cystic lesions. Such lesions are almost always benign, and can be satisfactorily treated by needle aspiration. On the other hand, a lesion that appears solid by echo scan is more likely to be a tumor.[42] Thermographic techniques are also useful in that cystic lesions are usually cold and solid tumors are warm on thermography. Although this is helpful in differentiating cysts from solid tumors, thermography cannot differentiate between benign and malignant lesions.[43] Soft tissue roentgenograms of the neck may show shell-like calcification, suggesting a benign cyst, or punctate calcification, which is more suggestive

TABLE 4.—*Differential Diagnosis of Thyroid Nodules*

Clinical Evidence	*Low Index of Suspicion for Thyroid Cancer*	*High Index of Suspicion for Thyroid Cancer*
History	Familial history of goiter Residence in area of endemic goiter	Previous therapeutic irradiation of head, neck, or chest Hoarseness
Physical characteristics	Older women Soft nodule Multinodular goiter	Children, young adults, men Solitary, firm, dominant nodule Vocal cord paralysis Enlarged lymph nodes Distant metastatic lesions
Serum factors	High titer of antithyroid antibody	Elevated serum calcitonin
Scanning techniques		
Uptake of ^{131}I	"Hot" nodules	"Cold" nodule
Echo scan	Cystic lesion	Solid lesion
Thermography	Cold	Warm
Roentgenogram	Shell-like calcification	Punctate calcification
Technecium flow study	Avascular	Vascular
Thyroxine therapy	Regression after 0.3 mg per day for three months or more	No regression

of cancer.[44] Metastatic lesions on scan or x-ray are strongly suggestive of malignant disease (Table 4).

Effects of Thyroxine Therapy

Nontoxic goiters are probably caused by impaired synthesis of thyroxine and hyperplasia secondary to excessive secretion of thyroid-stimulating hormone (TSH). Therefore, administration of thyroxine in sufficient doses to suppress secretion of TSH should allow regression of nontoxic goiters. This certainly occurs in most diffuse nontoxic goiters and in some multinodular goiters, whereas large cystic nodules will regress poorly.[45-47] There is evidence that many thyroid cancers, particularly papillary and follicular carcinoma, can be stimulated by TSH, and this technique is used in radioiodine therapy of advanced thyroid cancer.[48] There have been a few instances where metastatic lesions in the neck or in the lung have actually decreased in size or disappeared on suppressive thyroxine therapy.[49] On the other hand, most thyroid cancers, although they may not grow as rapidly during suppression of TSH by thyroxine, do not completely regress on such therapy. Therefore, the "suppression test" may be useful. In this procedure, L-thyroxine, 0.3 mg per day or its equivalent, is given for a period of three to six months, and the nodule is observed and measured carefully. If the nodule regresses in size and disappears, it is reasonably certain that it was not malignant. If it does not regress or grows during thyroxine therapy, then the suspicion of malignant disease is greater (Table 4).

Factors that contribute most to a high index of suspicion of malignancy are: history of previous therapeutic irradiation, a solitary firm nodule in a young person or a male patient of any age, a "cold" nodule on ^{131}I scan, and failure to regress on thyroxine therapy. Factors that suggest a benign lesion are: a soft nodule or a multinodular goiter, a "hot" nodule on scintiscan, and significant regression after thyroxine therapy.

Clinical Applications

Recently I had opportunity to summarize the records of a group of 158 patients who were treated according to the above plan (Table 5). In almost all patients who had diffuse goiter, regression occurred after thyroxine therapy. One patient could not tolerate thyroxine and could not be treated. One patient presented with a large, firm, diffuse goiter that increased in size during thyroxine therapy; on surgical excision the lesion was found to be lymphosarcoma of the thyroid gland. In most of the patients with multinodular goiters, regression occurred during therapy with thyroxine. Of the four patients in whom regression did not take place, malignant disease was found in one. About half the patients who had a dominant nodule in a multinodular goiter responded to thyroxine; three cancers were found among the six goiters that did not regress.

The patients with solitary nodules were divided into three groups—those with "hot" nodules, those with "cold" nodules highly suspicious of malignant change, and those with "cold" nodules not highly suspicious of malignant change. Three patients

TABLE 5. *Results of Therapy with Thyroxine in Patients with Thyroid Lesions*

Type of Lesion	Number of Patients	Thyroxine Therapy		Surgical Excision	
		Number Treated	Number Regressed	Number of Patients*	Number with Cancer
Diffuse	49†	48	47	1	1
Multinodular					
No dominant nodule	29	29	25	4	1
Dominant nodule	13	13	7	6	3
Single nodule					
"Hot"	11‡	8	5	1§	0
"Cold" and highly suspicious	24	0		24	8
"Cold" and less suspicious	32	32	19	13	2
TOTAL	158	130	103	49	15

*None of the patients with "cold" single nodules and a high index of suspicion of cancer received thyroxine; all other patients who had surgical excision had received thyroxine and the lesion had not regressed.

†One patient not treated with thyroxine.

‡Three patients not treated with thyroxine.

§Excision for cosmetic purposes.

with "hot" nodules received no treatment. Only one of the "hot" nodules was surgically removed; it was an adenoma. The incidence of malignant change among the "cold," suspicious nodules was 33 percent. About half the "cold," less suspicious, nodules responded well to thyroxine. Of the remainder, two of 13 were malignant. The total incidence of malignant change in the group operated upon was about 30 percent. The other lesions that were found were mostly adenomata.

Other Diagnostic Aids

The development of a simple blood test for the presence of thyroid cancer would be a great aid in diagnosis. Van Herle reported elevated levels of thyroglobulin in some patients with thyroid cancer.[50] Calcitonin, a hormone secreted by the parafollicular cells of the thyroid gland, has been found in high concentrations in the serum of patients with medullary carcinoma of the thyroid gland, and has been very useful in detecting patients with this rare type of thyroid cancer.[51,52] Needle biopsy of the thyroid has been proposed as a diagnostic technique,[12,53,54] but it has been more useful for the diagnosis of chronic thyroiditis than for thyroid cancer.[55,56] Thus, we are still left with largely clinical criteria for the differentiation of benign from malignant thyroid lesions before operation.

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Urinary Tract Infections in Children

Part I—Young Girls with Non-Refluxing Ureters

WILLIAM R. FAIR, MD
DUNCAN E. GOVAN, MD, PhD
GERALD W. FRIEDLAND, MD
ROY A. FILLY, MD
Stanford

This paper is the study of 144 girls with histories of urinary tract infection followed at the Stanford Medical Center who were found to be free of ureterovesical reflux. The mean age at onset of infection for the entire group was about four years and ranged from the first few months of life to age 10. Ninety-two percent of the 505 infection episodes in these children presented with symptoms referable to the lower tract, and bacterial localization studies confirmed that 85 percent of the infections were limited to the bladder. Escherichia coli was the most common organism isolated and most infections were caused by a pure culture of a single bacteria.

In only two of the 144 patients studied was there any evidence of upper tract damage related to infection. The possibility that these patients had reflux at an earlier age could not be discounted.

In response to short-term antibacterial therapy in 66 of the patients followed closely for an average of 40 months each, 20 percent of the patients had no further infections and 80 percent went on to recurrence. With each succeeding treatment an additional 20 percent of the patients were "cured," but the remainder experienced recurrent infections during the follow-up. This reinfection pattern supports the use of long-term antibacterial prophylaxis in all girls who have more than three or four recurrences of infections. Urethral dilation appeared to have no value in reducing the reinfection rate. While it appears that in the absence of ureterovesical reflux few, if any, of these children will go on to develop upper tract damage, long-term prophylactic suppressive medication can clearly be justified on the grounds of reducing patient morbidity.

THIS FIRST of three papers on the topic of urinary tract infection in children considers some of the problems encountered in diagnosing and treating (as well as preventing) these infections in female patients with non-refluxing ureters. The incidence of urinary tract infection in the newborn is much higher in boys than in girls,[1-4] but beyond the neonatal period urinary tract infections are rare in little boys.[2] Aside from the pronounced male preponderance in the newborn period as compared with older children, neonatal infections also differ in that they probably originate from a hematogenous rather than an ascending urinary tract mode of spread.[1] Thus, the most common problem encountered in pediatric urology beyond the neonatal age is recurrent infections in girls. As the following papers in this series will discuss in detail children with refluxing ureters, we will confine our remarks here to infections in little girls who have

This is Part 1 of a paper in three parts.

From the Department of Surgery, Division of Urology, and the Department of Radiology, Division of Diagnostic Radiology, Stanford University Medical Center, Stanford.

This study was supported in part by Research Grant No. 5 RO1 AI10668, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USPHS.

Dr. Fair is a Recipient of Research Career Development Award No. 5 KO4 A170107, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USPHS.

Dr. Filly is an Academic Trainee in Diagnostic Radiology, Grant No. GM 1707, National Institute of General Medical Sciences, National Institutes of Health, USPHS.

Reprint requests to: W. R. Fair, MD, Division of Urology, Department of Surgery, Stanford University Medical Center, Stanford, CA 94305.

been shown to be free of any obstructive lesions of the urinary tract and in whom voiding cystourethrograms have failed to show ureterovesical reflux.

Methods

The study population investigated consisted of 144 young girls with non-refluxing ureters evaluated at Stanford during the years 1961 through 1971. This number obviously does not represent the total number of pediatric patients evaluated at Stanford during that period. The vast majority of children seen at our center are not followed in our clinic but are referred back to their own physician after complete evaluation. Rather, this group was made up of 144 patients, all of whom had intravenous pyelograms and voiding cystourethrograms to exclude anatomical defects of the genitourinary tract, and were followed personally by one of us for at least 12 months. Most of the children were white and of middle class socio-economic background. Urine cultures, bacteriologic studies and localization techniques were performed as previously described.[5] In those patients where urethral calibration and dilations were performed the technique used was that described by Lyon et al.[6]

Results

Clinical Findings

• *Age at onset.* Chart 1 illustrates the age at the first infection. In most cases, the age given was obtained by history either from the parents or from the referring physician, and the patient was not seen by us during the first infection. The onset of the first infection was widely distributed from the first few months of life to age ten. The mean age of onset for the entire group was about four years and the median was slightly less than three years. In 54 percent of the group (78 of 144), the first infection was at the age of three years or younger.

• *Clinical presentation.* Chart 2 shows the clinical presentation of infections. We have considered those episodes presenting without fever, chills, flank or abdominal pain as bladder infections and those presenting with fever and chills plus or minus flank or abdominal pain as kidney infections. Ninety-two percent (465 of 505) of the infections in these 144 children presented with symptoms of lower tract involvement. Only 8 percent of the children had fever or signs referable to kidney involvement. A significant number of

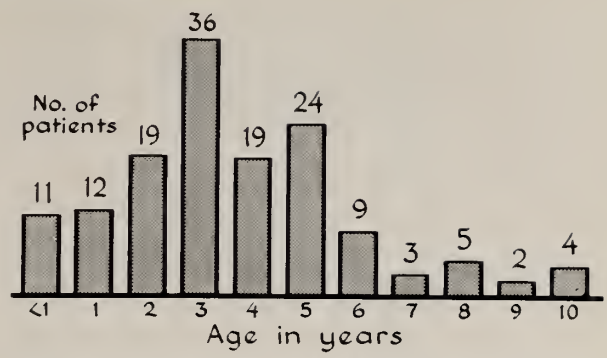

Chart 1.—Age at onset. The age at onset of first infection in 144 girls without vesicoureteral reflux, as obtained by history from the parents or referring physician. The mean age of the entire group was approximately four years and the median slightly less than three years.

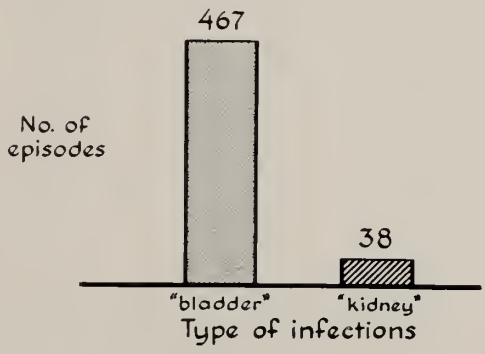

Chart 2.—Clinical presentation of type of infection. Those patients presenting with fever and chills, with or without flank or abdominal pain, were considered as having "kidney" infections. Patients without fever or chills were considered as having "bladder" infections.

those infection episodes included under the heading of bladder infections represent asymptomatic bacteriuria.

• *Nature of infecting organisms.* The organisms responsible for the infections encountered in our study were similar to those reported in other series.[1,2,7] The vast majority of infections were due to Escherichia coli, with smaller numbers due to Klebsiella, Proteus mirabilis, Streptococcus fecalis, and Pseudomonas (Chart 3). Only a small fraction of the infections was due to two or more organisms. Escherichia coli was also responsible for most of the kidney infections, identified as the etiologic agent in 34 of the 38 infections presenting with fever. No serotyping was done on the E. coli so it was not possible to differentiate between relapse and reinfection in these patients.

• *Localization of infection site.* In 47 of the patients in the study, upper tract bacterial localization studies were done. Results of these studies, done by cystoscoping the patient during an active

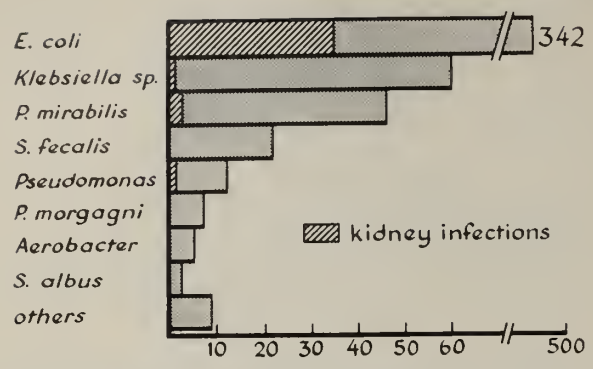

Chart 3.—Nature of infecting organisms. Escherichia coli was responsible for the majority of urinary tract infections as well as for most of those localized to the kidney. The vast majority of infections were due to a single strain of bacteria with only a small fraction caused by two or more organisms.

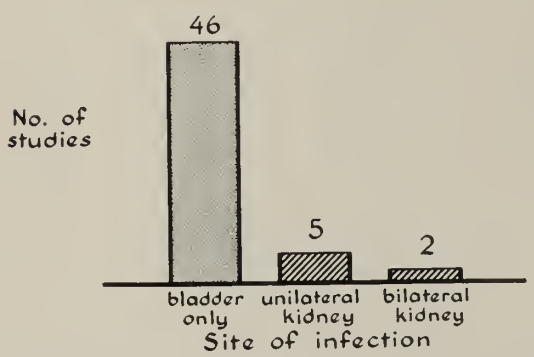

Chart 4.—The results of bacterial localization studies in 47 patients (53 studies). Bacteria could be recovered from one or both of the upper tracts in only seven of the 53 studies (15 percent).

infection and passing catheters up both ureters for the collection of serial urine specimens,[5] confirmed our clinical impression that most of the infections were localized to the bladder (Chart 4). In a few patients more than one study was done, accounting for the total of 53 studies in the 47 patients. Of the 53 studies, 46 localized the site of infection to the bladder, five suggested unilateral kidney involvement and in only two was there bilateral involvement of the kidneys.

Thus, we have a study population of young girls referred to our institution primarily with symptoms of lower urinary tract infection. E. coli was the most frequently found infecting organism and bacterial localization studies confirmed the clinical impression that most of the infections were limited to the bladder.

• *Urethral length and caliber.* Table 1 lists the urethral length measurement in 61 of the patients. In 54 of the 61 patients the urethra was between

TABLE 1.—*Pediatric Infection—Urethral Length*

Length (cm.)	*Number of Patients*
<1.5	0
1.5 - 2.0	29
2.1 - 2.5	25
2.6 - 3.0	3
3.1 - 3.5	2
3.6 - 4.0	2
TOTAL	61

All studies were done under general anesthesia before cystoscopy. The urethral length was measured by inflating a small Foley catheter and holding it and pulling it snugly against the bladder neck and marking the external meatus with a forceps. After the catheter was removed the space between the inflated balloon and the area of the external meatus was taken as the length of the urethra.

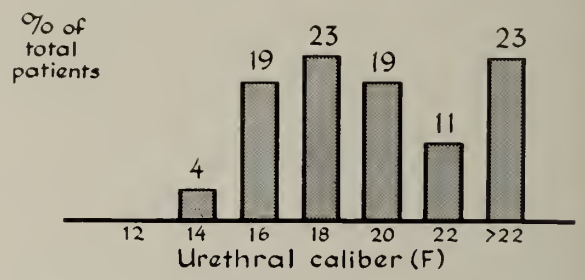

Chart 5.—Urethral caliber (French) as determined by use of Otis bulbs at the time of cystoscopy under general anesthesia.

1.5 and 2.5 cm long and in the remaining seven it was longer. Chart 5 gives the urethral caliber as determined by using Otis bulbs before cystoscopy with the child under general anesthesia. The mean urethral caliber was slightly greater than 18 French (Fr) and one of the children examined had a urethra measuring less than 14 Fr. These values are within the normal range for the age of the population involved.[8,9]

• *Radiologic abnormalities.* The radiologic assessments of those patients whose x-ray films were available for detailed examination will be discussed in full in part II of this series. In all children, both intravenous pyelograms and voiding cystourethrograms were done, but many films were not available for review at the time of this analysis. The presence or absence of renal change in the patients discussed in this paper was determined by reviewing the written x-ray reports. Only two of the 144 patients (three of 285 kidneys—1.1 percent) showed evidence of calyceal scars or atrophy either before or during the period of observation. One of these two patients actually showed the development of a scar in a previously normal pyelogram. When first seen by us, an intravenous pyelogram (IVP) showed evidence of

chronic pyelonephritis in the left kidney with a normal right kidney. During the course of follow-up the left calyceal scarring and atrophy progressed and the right kidney also developed radiographic changes characteristic of chronic pyelonephritis. Cystoscopic examination of this patient's bladder showed the ureteral orifices to be patulous with only a minimal suggestion of submucosal tunnels. We strongly suspect that she previously had vesicoureteral reflux although two cystourethrograms failed to show any abnormality. In addition, this patient had febrile episodes and flank pain accompanying several of her episodes of infection, which clinically indicated pyelonephritis.

In the other patient, unilateral renal scarring was present the first time an intravenous pyelogram was done, and the appearance of the kidney did not change during subsequent examinations. In only one instance did a normal kidney change to a scarred kidney during our follow-up period.

Treatment Considerations

• *Results of short-term treatment.* Various treatment regimens were carried out during the management of these patients. Some were treated with short-term antibiotic therapy or urinary acidification plus methenamine, others with long-term suppressive drugs, and still others received a combination of short-term treatment and long-term suppressive agents. Of the 144 children in the study we were able to select 66 followed for more than one year who were not treated with any long-term suppressive agents. These girls were followed for an average of 40 months, and treatment consisted of ten days of a specific antibacterial agent following diagnosis of an infection by urine culture. A patient was considered free of infection following treatment only if a sterile urine culture was obtained at least three to four days after all antibiotics were stopped. A variety of antibacterial agents were used; generally the choice was made on the basis of bacterial sensitivity results. The primary antibacterial drugs used for therapy were sulfas, penicillin-G and nitrofurantoin. Chart 6 shows the reinfection rate in children who were given short-term treatment for a specific infection and urine cultures indicated that the treatment was indeed successful. Of the 66 children with bacteriuria who were treated once, 75 percent went on to another infection at some time during the follow-up period. After treatment of this second infection, a certain percentage would again be apparently "cured" and not have another positive culture, but the majority went on to a third infection, and so on. The solid line in Chart 6 is the line that would be obtained if with each infection 20 percent of the girls never had another infection, and 80 percent would go on to have a recurrence—that is, 20 percent of the population were "extracted" from the pool at risk. The circles indicate the actual values obtained, and there is remarkable agreement between these figures and the theoretical 20 percent extraction ratio obtained by drawing a curve with each point 20 percent below the preceding level. Our findings tend to confirm previous observations[10] that every time we treat an infection in a population of girls without vesicoureteral reflux who hav recurrent infections, 20 percent of them have no further need of treatment but 80 percent will have another infection.

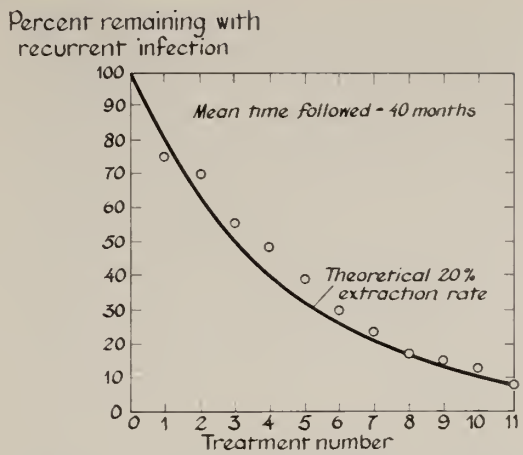

Chart 6.—The results of short-term antibacterial therapy in 66 children. The circles indicate the percentage of girls who went on to another infection after receiving treatment. The solid line indicates the theoretical 20 percent extraction ratio obtained by drawing a curve with each point 20 percent below the preceding value.

TABLE 2.—*The Effect of Urethral Dilation—29 Patients*

	Patient Months Followed	*Number of Infections*	*Patient Months/ Infection*
Pre-dilation	1,037	180	5.8
Post-dilation	783	143	5.5

Effective urethral dilation on the infection recurrent rate. Dilation was done as described by Lyon and Tanagho.[6]

• *Results of urethral dilation.* Twenty-nine patients in the study had urethral dilation done at Stanford and had sufficient follow-up to document bacteriologically the effect of the procedure on the subsequent course (Table 2). The 29 patients were followed for an average of about 36 months

each before dilation, for a total of 1,037 patient months. During this time 180 infections were diagnosed as occurring in the 29 patients, an average of one infection every 5.8 months. Following urethral dilation the 29 patients were followed for an average of 27 months each or a total of 783 patient months. One hundred and forty-three urinary tract infections occurred during this follow-up, an average of one infection every 5.5 patient months. Hence, in these retrospective results it appears that urethral dilation had no effect in reducing the rate of infection in this group.

Discussion

This study is a retrospective analysis of some clinical and therapeutic observations in a population of 144 predominantly white girls 18 months to 14 years of age evaluated at Stanford University Medical Center for documented urinary tract infections. All patients in the study had an intravenous pyelogram and a voiding cystourethrogram, and were followed in our clinics for more than 12 months. No patients with vesicoureteral reflux were included in this analysis.

The age at onset of initial infection in this group of girls with non-refluxing ureters was four years. In a previously reported[11] group of patients with reflux, similar in age and socio-economic status, who were evaluated at our institution, the mean age at onset of urinary tract infections was 3.2 years. The earlier onset of apparent symptomatic disease in patients with refluxing ureters, as compared with patients with non-refluxing ureters has also been noted by Winberg and associates.[12] Our figures also agree quite closely with those of Smellie and Normand,[13] who found a mean age of 4.3 years in a group of children evaluated for recurrent urinary tract infection. The indication that there is a higher peak incidence of symptomatic infections in the third or fourth year of life is sharply at odds with results of screening studies that indicate infections are at their peak in the first year of life.[14,15] Several possibilities are suggested to explain this apparent discrepancy:

- Most urinary tract infections in patients under one year of age are not diagnosed as being urinary tract infections. In the few instances where this factor was studied, it was found to be the most likely possibility, and if diagnosis of urinary tract infection were made on clinical grounds alone, it could easily be missed. In the University College Hospital group[15] only 9 percent of patients less than 12 months of age who subsequently were proved to have a urinary tract infection were diagnosed as having an infection on clinical grounds.
- The second reason that there seems to be a higher incidence in neonates than in older children may be that younger children respond very well to therapy and have fewer recurrences. In a report from Sweden[14] it was noted that only 26 percent of children with infections in the neonatal period had recurrences over the next few years.
- The third and perhaps the most likely possibility is that there is a relatively high incidence of false positive urine cultures obtained in the neonatal age group. Abbott[16] did suprapubic bladder aspirations in 1460 infants who had a "clean catch" urine specimen collected (by a specially trained nurse) between the third and sixth days of life. He found that of 1,170 children whose urine specimens had a bacterial count in excess of 10,000 colonies per milliliter, only 14 were found to have bacteriuria by the bladder puncture technique. In a similar study Edelmann, et al[17] found that of 11 infants with an initial urine culture showing greater than 10^5 organisms per milliliter, only one had documented bacteriuria by repeat culture.

The organisms responsible for infection in the series here reported are similar to those reported in other series[1,2,7,18] with E. coli being predominant. Of particular interest is the very small number of patients with two or more infecting organisms, further confirming the observation that most urinary infections are due to only one strain of bacteria. It was not possible to distinguish between upper tract and lower tract disease on the basis of the infecting organisms.

The vast majority of our patients presenting with urinary tract infections did not have fever, which we feel is the most accurate clinical indicator of a kidney infection. Bacterial localization studies indicated that there was involvement of one or both kidneys in only seven of the 53 studies. These figures are in decided variance with the results obtained in adult females.[5] The reason for this difference is not readily apparent.

Of note was the very low incidence of calyceal scarring or cortical atrophy noted on radiologic examination of the patients. In two of the 144 patients, there was evidence of scars or atrophy of cortical tissue (three of the total of 285 kidneys studied). In only one of these kidneys did the scars develop while the patient was being followed by us. Definitely abnormal orifices were observed cystoscopically in this patient, but two voiding

cystourethrograms (done while the urine was sterile) failed to demonstrate reflux. The possibility that in this child reflux was present during an episode of infection cannot, of course, be discounted. The other child had unilateral pyelonephritic changes which were present at the time the initial intravenous pyelogram was performed; these findings did not progress despite continued lower tract infections. Hence, there is very little evidence from our study that urinary tract infections in girls who do not have vesicoureteral reflux will lead to progressive scarring or atrophy of the kidney.

A useful discussion of urinary tract infections, particularly in children, must include the relative merits of short-term and long-term treatment. Also, it is impossible to assess the results of such treatment by a retrospective analysis. However, some recent studies in the literature may shed some light on the problem of duration of treatment in urinary tract infections. Bergström and associates[14] made comparisons between two different treatment regimens in little girls who had either a first or a second urinary tract infection uncomplicated by obstructive urologic abnormalities. The 279 girls in the study were treated for either ten days or 60 days with sulfasoxazole (Gantrisin®). The patients were carefully followed for a period of one year with good bacteriologic control. Two-thirds of the girls in each group had no recurrence during that time, and there was no difference between those treated for ten days and those treated for 60 days. The only real difference was that the group treated for two months had a slightly higher percentage of asymptomatic recurrences than those receiving the shorter treatment. Thus, there appears to be no real advantage in treating an acute infection for two months instead of ten days. However, when drugs are given for longer periods (6 to 12 months for each infection) it does appear that the prolonged therapy reduces the incidence of recurrences. Normand and Smellie[19] gave maintenance chemotherapy for 6 to 12 months to 50 children such as those in our series with normal x-ray studies. In this group 85 percent had no recurrences either during therapy or during follow-up for an average of a year and a half after therapy was discontinued. This finding underscores the problem pointed out by Kunin:[20] The real problem is identifying those children who are susceptible to recurrent infections and perhaps directing long-term therapy to that group.

The most interesting observation found in our analysis was the fate of short-term treated children followed for an average length of time of 40 months. Each of the patients in this study received ten days of a specific antibacterial agent at the time the infection was diagnosed; no long-term suppressive medication was given to this group. As shown in Chart 6, our results confirm the earlier observations of Kunin[10,20] which indicate essentially that each time we treat a group of children with urinary tract infection, 20 percent of patients will have no further difficulties, but 80 percent will go on to have another infection. If the remaining 80 percent who develop a second infection are again treated, another 20 percent of that population will be extracted out as cured (but 80 percent of that group will still go on to develop another infection). Obviously as we go down to the tenth or eleventh infection, we are getting down to a very small group indeed, but it is this group of patients that it would be most rewarding to identify for long-term suppressive treatment. Similarly, one could thus obviate long-term suppressive treatment for every child with urinary tract infection, as the majority will have no more than three or four infections and then no more during childhood. At this point it is important to realize that in discussing the prevention of recurrences we are for the most part talking about preventing *reinfection* rather than *relapse*. Kunin[20] and Bergström et al[21] have shown that 85 percent of urinary tract infections are new infections caused by a different organism each time. From this it is clear that long periods of treatment are simply preventing reinfections and not eradicating relapses due to inadequate treatment.

As to the effects of urethral dilation, controversy still exists concerning the efficacy of surgical manipulation (urethral dilation or internal urethrotomy) in the treatment of recurrent urinary tract infections. The urethral calibrations measured in our study are considered normal values for the age of the population involved.[8,9] Graham, King, Cropp and Uehling[8] observed that in 191 girls with urinary infections the caliber of the distal urethra was larger than it was in 76 normal children who had had no previous urinary tract infections. From these and other carefully documented studies it seems apparent that the diameter of the urethra bears little relationship to the propensity of girls to acquire urinary tract infections. Studies showing that such manipulation is beneficial must be interpreted carefully, for often phy-

sicians who treat the urethra in this way combine that treatment with administration of chemotherapeutic agents at least for a short time following the manipulation. The results of Kunin,[10] confirmed by us in this study, prove that medication alone will produce a long-term cure in 20 percent of young white girls whether the infection is the first or the tenth. Also, in many of the previously reported studies on this subject, urine cultures were not done to determine whether or not infection was present. In the 29 patients we observed before and after dilation, we saw no beneficial effects of the procedure.

One of the best and perhaps the only prospective study in the literature dealing with this problem was recently published by Kaplan, Sammons and King.[22] They designed a prospective study to compare the effect of a drug alone, a drug plus urethral dilation and a drug plus internal urethrotomy in a total of 49 patients. Following cystoscopy with or without manipulation, all patients were given nitrofurantoin for a total of three months. Eighteen months after completion of therapy, approximately one-third of those treated with the drug alone or the drug plus dilation had remained free of infection. These investigators also found that there was a higher rate of reinfection when the drug and internal urethrotomy were combined. The reasons for this are unknown. This well performed and bacteriologically documented study must be considered the best prospective study in the literature dealing with the problem of whether or not urethral manipulation has any role in the treatment of recurrent infections.

One last note of particular interest is the similarity between women who have recurrent urinary tract infections and young girls with nonrefluxing ureters. The first similarity between these two groups is that the major problem in both is clearly one of recurrence, with a new infection each time rather than a relapse from a chronic focus of infection. McGeachie,[23] studying urinary tract infections in women, found more than 80 percent of infections were caused by a different organism each time. These figures are remarkably consistent with those reported by Kunin[2] and Winberg et al[12] in little girls, and lead us to believe that the problem of reinfection has striking similarities in adults and children. The finding that 80 to 90 percent of all infections were caused by a different organism each time eliminates the possibility that the majority of infections were caused by a relapse from a chronically infected focus.

In a careful study of the perineal flora of normal women[24] we found that 90 percent of women who have no history of urinary tract infections have no Gram-negative organisms whatsoever on the perineum. Stamey et al[25] have also shown similar results in a series of little girls visiting a pediatrician's office for routine physical examinatons. These girls, who had no history of past urinary tract infections, supplied urine specimens for culture by simply voiding into a sterile cup while sitting on the back of a toilet seat. No perineal wash was used before the specimen was voided, and no specially trained urologic personnel were present at the time of voiding. The child voided the first portion of the urine into one cup (VB_1), and as she continued to void, the midstream urine (VB_2) was obtained in the usual manner. Two-thirds of the girls had no Gram-negative bacteria present on cultures of the first specimen. Most of the cultures that did grow Gram-negative bacteria had fewer than 1,000 colonies per milliliter; only four of the group of the 117 children studied had more than 5,000 Gram-negative bacteria per milliliter in the VB_1 specimen. When repeat cultures were taken in each of these four cases, all had VB_1 colony counts much lower than 1,000 bacteria per milliliter. It is clear then, that under normal conditions the perineum both of women and young girls is free of Gram-negative organisms. It is also clear that reinfection rather than relapse is a major cause of recurrence in both women and children. The potential for infections is essentially the same for children and adults.

These similarities between the two groups could lead one to a conclusion that long-term antibacterial suppression in children with recurrent infections and abnormal perineal flora may be of value in reducing the overall reinfection rate, just as appropriate antibiotics at the time of sexual intercourse have been effective in reducing reinfections in women.[26]

The question of which drug should be used for suppression is not clearly settled. Lincoln, Lidin-Janson and Winberg[27] used sulfasoxazole in their treatment trials. Fortunately, in that group they also did serotyping of the E. coli in the vaginal and fecal flora, and observed that sulfa changed the fecal flora to sulfonamide-resistant organisms within a short time. Nitrofurantoin, on the other hand, was shown to have relatively little effect on fecal flora, and in a consideration of long-term suppressive medication this drug would seem worthy of trial. Since active children appear to

have bladder bacteriuria as a result of intermittent entry of perineal Gram-negative bacteria into the bladder, a treatment regimen such as one tablet of nitrofurantoin nightly might be as effective in preventing recurrences in children as it has been in women.[28] We hope to answer these questions in a prospective study.

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Urinary Tract Infections in Children

Part II — Roentgenologic Aspects

ROY A. FILLY, MD
GERALD W. FRIEDLAND, MD
DUNCAN E. GOVAN, MD, PhD
WILLIAM R. FAIR, MD
Stanford

Roentgen findings in 107 girls under the age of ten years who had proven recurrent urinary tract infections were analyzed. From the excretory urograms done on these children, renal and pelvocalyceal outlines were accurately traced. Subsequently, renal length and parenchymal thickness at multiple points were measured. The presence or absence and grade of reflux were determined by voiding cystourethrography. Finally, the clinical history was correlated with the roentgen findings.

With three exceptions, scarring and clubbing in the presence of infection occurred only in refluxing renal units. Kidneys exposed to a higher grade of reflux more frequently showed scarring and clubbing ($p<0.001$). Seventeen out of 40 renal units either developed or had increase in clubbing and scarring while the patients were being followed. After surgical correction of reflux, 16 of 24 previously clubbed and scarred kidneys showed progression of the lesions, usually within 24 months after operation. All children whose kidneys showed progression after surgical operation had experienced an episode of acute urinary infection with chills and fever before operation.

No significant difference existed in the age at clinical onset of infection in patients with ureteral reflux with or without roentgen evidence of clubbing and scarring. This study documents the close relationship between clubbing and scarring and reflux in the presence of urinary infection in infants and children.

THIS, THE SECOND of three papers discussing urinary tract infections in infants and children, presents the radiological findings in children with non-refluxing ureters, children with refluxing ureters treated medically and children with refluxing ureters treated surgically.

The purpose of this paper is to answer several questions:

- Is there a relationship between clubbing and scarring seen on excretory urograms made on children with recurrent urinary tract infection and the presence or absence of reflux?
- If so, is there a relationship between the grade of reflux and clubbing and scarring?
- Do normal kidneys become clubbed and scarred, and does pre-existing clubbing and scar-

This is Part II of a paper in three parts.

From the Department of Surgery, Division of Urology, and the Department of Radiology, Division of Diagnostic Radiology, Stanford University Medical Center, Stanford.

This study was supported in part by Research Grant No. 5 RO1 AT10668, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USPHS.

Dr. Fair is a Recipient of Research Career Development Award No. 5 KO4 AI70107, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USPHS.

Dr. Filly is an Academic Trainee in Diagnostic Radiology, Grant No. GM 1707, National Institute of General Medical Sciences, National Institutes of Health, USPHS.

Reprint requests to: G. W. Friedland, MD, Department of Radiology, Stanford University Medical Center, Stanford, CA 94305.

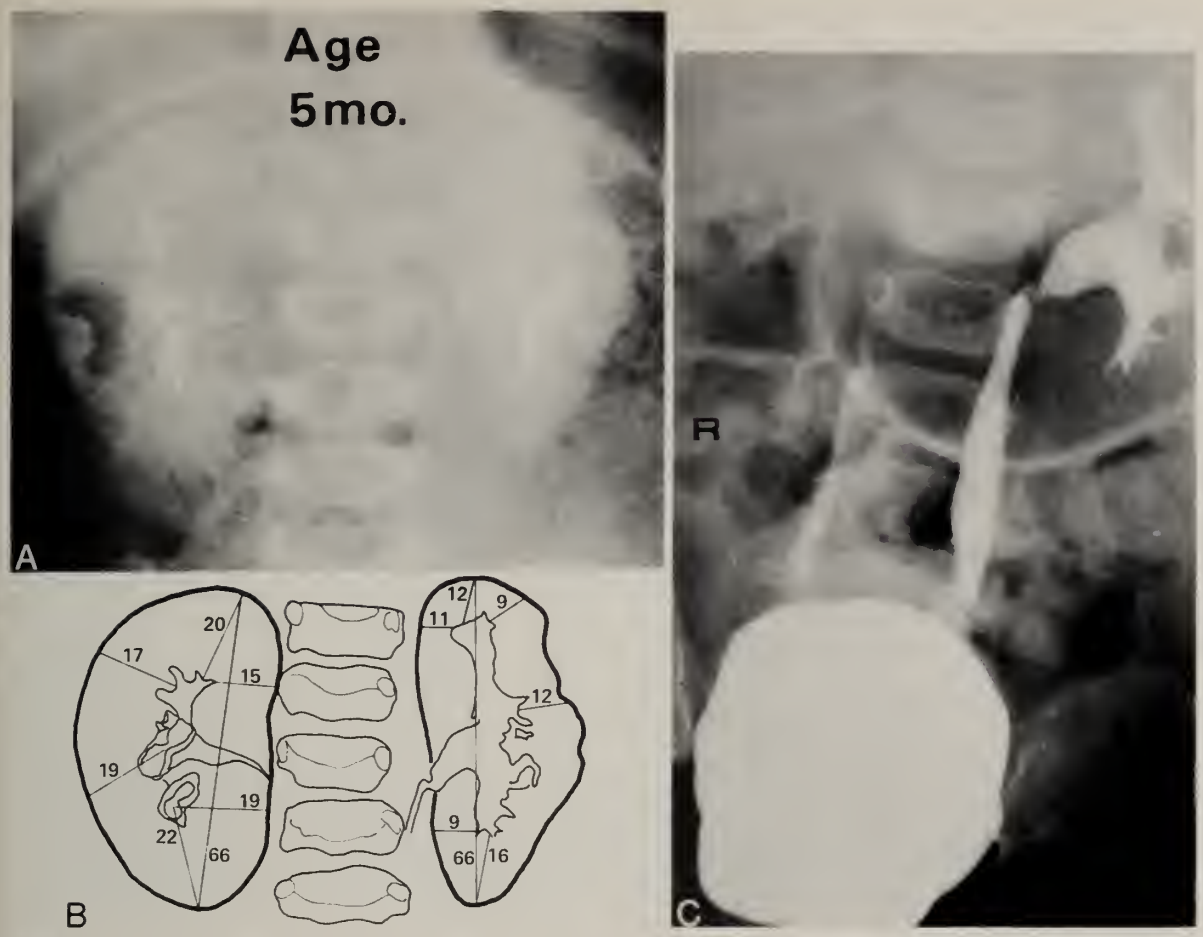

Figure 1.—Case of a five-month-old girl who had a documented urinary infection associated with a high fever at the age of three months. **(A)** Excretory urogram. The right kidney appears normal. The left kidney is irregular, with definite clubbing and scarring in its upper pole. **(B)** Tracing of the excretory urogram, demonstrating the measurements which were made. **(C)** Voiding cystourethrogram, grade II reflux on the left, grade I on the right.

ring progress (a) in non-refluxing kidneys, (b) in refluxing kidneys, (c) in previously refluxing kidneys following surgical correction of reflux?

- Does clubbing and scarring develop more frequently in children with refluxing ureters if the infections begin at an early age?

Materials and Methods

Only patients the radiologists personally examined are included in this study. Therefore, the number of patients who are discussed in this paper is less than the number discussed in the two other clinical papers of this trilogy. Our series consists of 107 girls under the age of ten years. Among them they had 210 kidneys, 103 right and 107 left; and 145 of the kidneys were normal, while 65 were clubbed and scarred. There were 110 refluxing ureters.

Each patient had one or more voiding cystourethrograms. We graded the reflux according to the following scale (Figures 1C and 3C and Table 1):

0 = no reflux
I = reflux into the ureter but not the renal pelvis
II = reflux into both the ureter and the renal pelvis, but without any dilatation of either the ureter or the renal pelvis
III = reflux into the ureter and renal pelvis, with dilatation of ureter and renal pelvis

If the patient had more than one voiding cystourethogram, we noted for statistical correlation only the worst grade of reflux observed in the patient at any time. Each patient, furthermore, had at least one excretory urogram more than one year after the clinical onset of infection. Many patients had several excretory urograms. On each excretory urogram, we carefully traced the renal outline and the pelvocalyceal systems on each side. We then measured the thickness of the renal parenchyma at multiple sites. Finally, we measured the

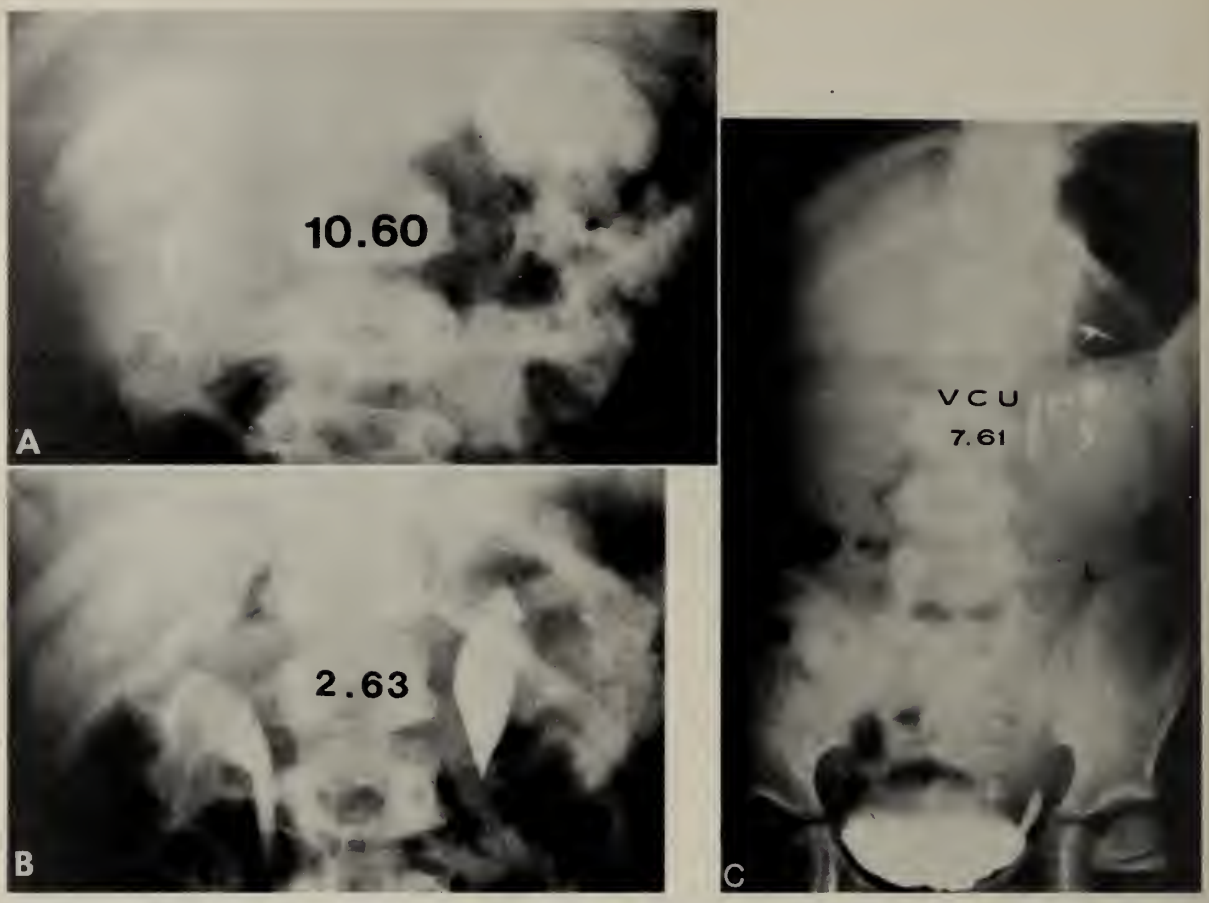

Figure 2.—Case of a three-year-old girl whose first documented urinary infection occurred at the age of two years (October 1959). Between October 1959 and July 1961 she had five documented urinary infections, three of which were associated with high fever. The left ureter was reimplanted in August 1961. **(A)** Excretory urogram, October 1960. The right kidney appears normal. Gas and stool obscure much of the left kidney, but the parenchymal thickness in its upper pole is within normal limits. **(B)** Excretory urogram, February 1963. The left upper pole has scarred. The opaque medium visible along the medial margin of the upper pole was present on the preliminary film. **(C)** Voiding cystourethrogram, July 1961. This radiograph was made with patient in upright position after she had ceased voiding. Barium was used as the contrast medium. Apart from refluxed contrast medium within the left pelvocalyceal system and ureter, some barium has escaped into the lymphatic chain (long, thin linear streaks) and the renal parenchyma.

renal length and noted the presence or absence of clubbing and scarring and its location (Figure 1B).

After all the radiological observations had been made, we correlated the clinical features of each patient with her radiological findings. The data were analyzed as follows: Because a patient may have had grade III reflux with clubbing and scarring on one side and no reflux with a normal kidney on the opposite side, we decided to analyze the data in "renal units"—that is, by separate kidneys and ureters, rather than by patients. These renal units were divided into three groups:

A. Non-refluxing renal units in patients who had recurrent urinary tract infections treated medically
B. Refluxing renal units in patients who had recurrent urinary tract infections treated medically
C. Previously refluxing kidneys with long-term postoperative follow-up

The patients who had reflux surgically corrected were studied only to find out whether they showed any development of new scars or progression of previous scars following operation, and also how long after operation this progression occurred.

Results

Non-Refluxing Renal Units

There was a total of 100 non-refluxing renal units (Table 2). These 100 renal units were distributed as follows:

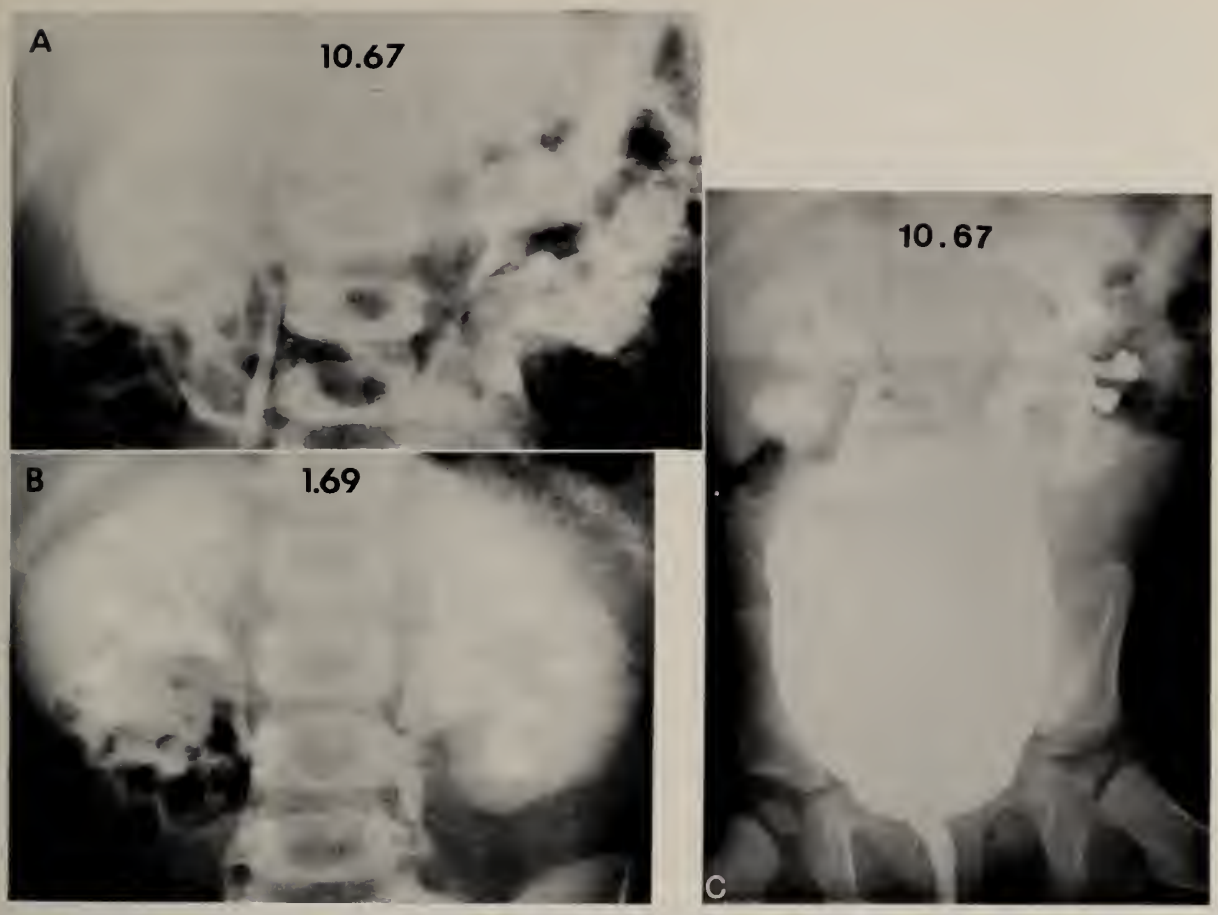

Figure 3.—Case of a four-year-old girl (October 1967) with recurrent urinary infections. **(A)** Excretory urogram, October 1967, demonstrates clubbing and scarring throughout the right upper pole. Following this examination, bilateral ureteral reimplantation was carried out. **(B)** Excretory urogram, January 1969, shows bilateral progression or development of clubbing and scarring in the areas of intra-renal reflux demonstrated on the previous voiding cystourethrogram. **(C)** Voiding cystourethrogram using an iodinated contrast medium demonstrates bilateral grade III vesicoureteral reflux and bilateral intra-renal reflux.

1. Non-refluxing kidney opposite a refluxing kidney subsequently surgically corrected: 16 kidneys
2. Non-refluxing kidney opposite a refluxing kidney treated medically: 17 kidneys
3. Kidneys in patients with recurrent urinary infections without reflux on either side, treated medically: 67 kidneys

Thirty-three out of the 100 non-refluxing kidneys were opposite refluxing renal units. This serves as an internal control. We were able to observe the effect of urinary tract infection on two kidneys in the same patient, one of which, for example, was refluxing and the other not.

We examined the radiographs of these 100 renal units to determine whether they appeared clubbed and scarred. To make this final determination, we noted the appearances of the last excretory urogram we had made in each patient. If the patient had only one excretory urogram, we included this in our series only if at least one year had elapsed between the first urinary infection and the examination. At the time of the final analysis, 97 of these non-refluxing renal units were normal, whereas three showed evidence of clubbing and scarring. Table 1 includes these data.

We followed 16 of these 100 renal units with multiple examinations. On the initial excretory urogram 15 renal units appeared normal and one appeared clubbed and scarred, whereas on the final excretory urogram, at least one year after the initial examination, new clubs and scars had developed in two previously normal kidneys (13.3 percent), and the one clubbed and scarred kidney showed progression of these abnormalities.

Two of the renal units in which clubbing and scarring progressed belonged to the same patient; one kidney was initially normal and the other initially clubbed and scarred. At cystoscopy, interestingly, this patient's ureteral orifices appeared

gaping and widely separated, with ureteral tunnels short or absent. This led us to suspect strongly that these ureters had previously refluxed. The final normal non-refluxing renal unit in which a scar developed belonged to a patient whose opposite kidney showed grade III reflux.

Refluxing Kidneys Treated Medically

There were 110 refluxing renal units (Table 3). Some patients are included who eventually underwent an anti-reflux procedure. We included them only if they had received more than one year of medical therapy before operation. Of these 110 refluxing renal units, 62 were clubbed and scarred, and 48 were normal.

We analyzed what effect the grade of reflux had on the presence of clubbing and scarring. Table 1 contains all the refluxing and non-refluxing renal units from the entire radiological series and it reflects our interpretation of each patient's final radiographic examination. As before, if a patient had only one excretory urogram, it was employed for analysis only if more than one year had elapsed from the initial urinary tract infection to the time of examination. As can be seen from Table 1, the higher the grade of reflux, the more likely it was that a kidney would show clubbing and scarring. These data were analyzed statistically, and the relationship between the grade of reflux and the propensity to develop clubbing and scarring was statistically significant, using the Student t test ($p<0.001$).

TABLE 1.—*Relationship Between the Grade of Reflux and Presence or Absence of Clubbing and Scarring*

STATE OF KIDNEY	0	I	II	III
NORMAL	97	20	17	11
CLUBBED AND SCARRED	3	6	17	36
UNGRADED REFLUXERS (3)				

TABLE 2—*Group A: Non-Refluxing Kidneys*

Renal Morphology	*Right*	*Left*	*Total*
Clubbed and Scarred	2	1	3
Normal	50	47	97
Total Non-Refluxing Kidneys	52	48	100

TABLE 3.—*Group B: Refluxing Kidneys Treated Medically*

Renal Morphology	*Right*	*Left*	*Total*
Clubbed and Scarred	33	29	62
Normal	18	30	48
Total Refluxing Kidneys	51	59	110

TABLE 4.—*Summary of the Findings in the Non-Refluxing and Refluxing Kidneys*

Group	*Clubbed and Scarred*	*Normal*	*Total*
(A) Non-Refluxing	3	97	100
(B) Refluxing	62	48	110

We then examined the eventual fate of 40 renal units followed radiologically for at least one year (average 3.8 years). At the time of the initial examination, 16 of these renal units were normal, and 24 were clubbed and scarred. At the time of the final examination, 14 were normal and 26 were clubbed and scarred. That is to say, 2 out of 16 (12.5 percent) changed from normal to clubbed and scarred. Fifteen of the 24 previously scarred renal units (62.5 percent) showed progression of clubbing and scarring. No progression of clubbing and scarring occurred in 9 out of 24 (37.5 percent) of these renal units. Significantly, as is discussed in detail in Parts I and III of this trilogy,[1,2] the infections in those patients who had progression of lesions were poorly controlled; where the infection was well controlled, there was no progression. In addition, the higher the grade of reflux, the more likely progression was to occur. This subject is discussed in detail elsewhere.[3]

In summary, we examined 100 non-refluxing kidneys, of which 97 were normal and three clubbed and scarred, and 110 refluxing renal units, of which 62 were clubbed and scarred and 48 were normal (Table 4). Thus, with three exceptions, clubbing and scarring occurred only in patients with refluxing renal units. Two of the three non-refluxing renal units with clubbing and scarring were cystoscopically observed to have abnormal ureteral orifices, suggesting that reflux had occurred intermittently at some time. The remaining one of the three was opposite a grade III refluxing kidney.

Refluxing Renal Units Treated Surgically

During the time spanned by this study, the urologists reimplanted 105 ureters. Radiologists in

our department, however, personally performed long-term follow-up examinations on only 37 of these renal units. None of these renal units refluxed postoperatively. This group was approached differently from the previous two groups in that we analyzed these renal units only for the presence or absence of progression. These 37 renal units were followed radiologically with multiple examinations for longer than one year postoperatively (average 3.3 years). Of these, 13 were normal at time of operation and remained normal afterward, whereas 24 were clubbed and scarred before and after operation. No normal kidneys, therefore, became clubbed and scarred after operation. On the other hand, 16 of 24 kidneys (66 percent) that were clubbed and scarred before operation showed progression of those abnormalities after correction of reflux. Except for three cases in which clubbing and scarring occurred more than two years after operation (Chart 1), all cases showed progression within 24 months. All patients with progression within 24 months after operation had had an episode of acute urinary infection, with chills and fever, immediately before the procedure. Three patients in whom clubbing and scarring progressed more than two years after operation also had had episodes of chills and fever 18 months to two years before the progression.

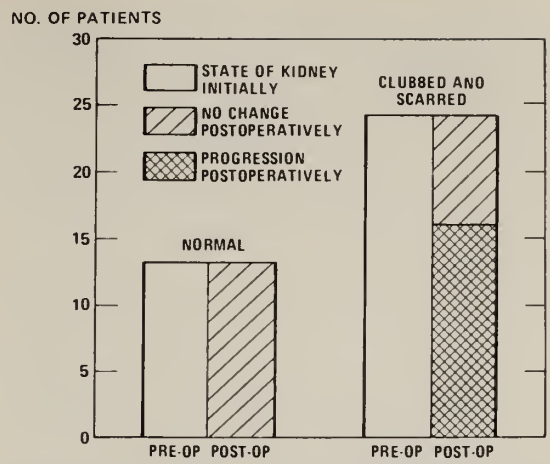

Chart 1.—Development and progression of clubbing and scarring following successful surgical reimplantation of ureters.

Age at Clinical Onset of Infection and Scarring in Refluxing Kidneys

The histogram shown in Chart 2 was constructed by comparing the ages at assumed clinical onset of infection for refluxing normal kidneys and refluxing clubbed and scarred kidneys. As the histogram shows, there was no difference ($p<0.001$).

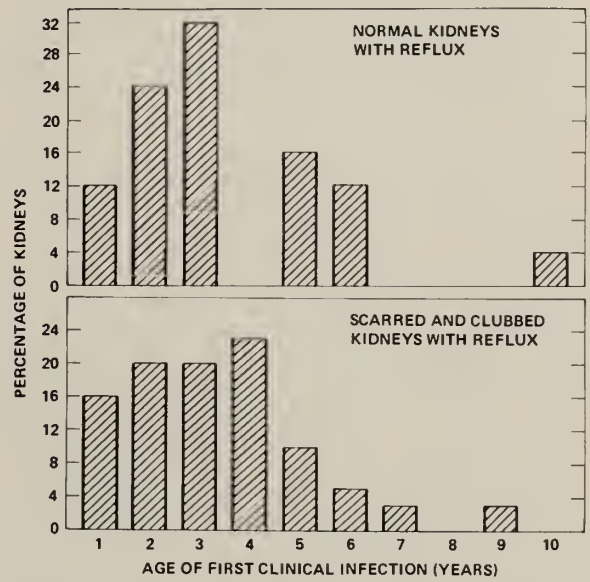

Chart 2.—Age at stated clinical onset of infection in refluxing kidneys.

Discussion

In this discussion we will try to analyze our results in order to answer the questions which were posed in the introduction.

- *Is there a relationship between clubbing and scarring seen on excretory urograms made on children with recurrent urinary tract infections and the presence of reflux?*

Our data (Tables 2, 3 and 4) have shown that, with three exceptions, clubbing and scarring occurred only in refluxing kidneys, which corroborates the results reported by several other observers;[5-22] but two of our three exceptions were of interest in that abnormal ureteral orifices were seen at cystoscopy. This suggests that these two renal units were intermittently refluxing[23] but that the voiding cystourethrogram was not performed at a time when reflux was occurring. There may be a quite simple explanation for this. It is our practice to wait at least two weeks (until the infection has been cleared with appropriate antibiotic therapy) before doing a voiding cystourethrogram, in order to avoid septicemia as a complication of the procedure.[24] It is therefore possible that these two kidneys were refluxing at the time of the acute infections but that reflux had ceased by the time the voiding cystourethrograms were done. Importantly, the incidence of reflux and

renal clubbing and scarring is high, according to various studies in the literature. Recent studies give 1 in 200, 1 in 500, and 1 in 180 as the incidence of clubbing and scarring in children.[25]

• *Is there a relationship between the grade of reflux and the presence or absence of clubbing and scarring?*

Our data (Table 1) clearly demonstrate that the higher the grade of reflux, the greater the likelihood of clubbing and scarring ($p<0.001$), using the Student t test. However, despite this clear statistical relationship, it was interesting to note that six kidneys with grade I reflux had clubbing and scarring, while 11 renal units with grade III reflux were normal. We wish to stress, therefore, that there are definitely some exceptions to the rule. The relationship between the grade of reflux and the presence or absence of clubbing and scarring has been suggested previously by several other observers,[6,15] but none of them were able to prove it statistically.

• *Do normal kidneys become clubbed and scarred, and does pre-existing clubbing and scarring progress?*

Some radiologists[26,27] do not believe that normal kidneys become clubbed and scarred or that clubbing and scarring progresses even in the presence of reflux. This complex issue is discussed in two separate reports.[3,5] However, our findings show that four normal renal units (two refluxing, one probably refluxing, and one non-refluxing) which were followed carefully radiologically became clubbed and scarred. In 17 of 40 renal units clubbing and scarring either developed or increased while the patients were being followed medically (Figures 2 and 3). Additionally, 16 out of 24 previously clubbed and scarred kidneys showed progression of clubbing and scarring following correction of reflux (Chart 1). Other investigators have also documented the development and progression of clubbing and scarring in children with both refluxing ureters and urinary infection.[6-22] After carefully documenting the date of infection and the subsequent development of clubbing and scarring, we found that it may take up to two years for clubbing and scarring to develop fully. Hodson reported a well-documented case in which a renal scar continued to contract for 15 months.[9] In reference to the 16 renal units showing progression postoperatively, it is of great interest to note that, with only three exceptions, the progression occurred within the first 24 postoperative months. In each instance, an episode of clinical pyelonephritis preceded operation. It is quite likely that the observed deterioration related to the preceding infectious episode rather than to the surgical procedure.

Three patients in whom we demonstrated intrarenal reflux[11,25,28-30] showed progression of clubbing and scarring in the areas of intrarenal reflux (Figures 2 and 3). Other investigators have noted this association[11,25,30] This concept is discussed in detail in the third paper of this trilogy.[2]

• *Does clubbing and scarring develop more frequently in children with refluxing ureters if the infections begin at an earlier age?*

Our data (Chart 2) show no correlation between the presence of clubbing and scarring in children with refluxing ureters and the age at clinical onset of urinary infection. We must point out, however, that it was very difficult to determine when a child had had the first urinary infection. Since often either the mother or the infant's physician may miss the first urinary infection, the stated time of initial onset may be inaccurate. On the other hand, there is no reason to suspect that the reported clinical onset in either the patients with clubbing and scarring or in those with normal kidneys would be uniformly biased toward earlier or later occurrence. If anything, one would suspect that the child with clubbing and scarring is the child who is likely to have had the more severe urinary tract infections and who would therefore be brought to the attention of the mother or the physician more quickly than children without such lesions. If one weighs all these factors, it seems unlikely that urinary infections began any earlier in those with scarred than in those with normal kidneys.

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Urinary Tract Infections in Children

Part III—Treatment of Ureterovesical Reflux

DUNCAN E. GOVAN, MD, PhD
WILLIAM R. FAIR, MD
GERALD W. FRIEDLAND, MD
ROY A. FILLY, MD
Stanford

Of 134 girls with demonstrable ureterovesical reflux, 61 (105 ureters) had the reflux surgically corrected with an overall surgical cure rate of 97 percent. In the remaining 73 children (112 ureters), the reflux was treated conservatively with medical management alone. During the follow-up period no significant differences were demonstrated in the overall incidence of urinary tract infection; two years following corrective operation or medical treatment more than 50 percent of both medically and surgically treated children were still experiencing infections. A pronounced decrease, however, occurred in the incidence of clinical pyelonephritis among the surgically treated group. Following correction of reflux, the incidence of pyelonephritis was similar in both medically and surgically treated cases and was approximately the same as that found in a comparable group of children without reflux.

In approximately two-thirds of refluxing renal units in which there was evidence of clubbing and scarring before medical or surgical therapy, deterioration progressed during the follow-up period. In most of these cases infection control was felt to be inadequate with episodes of clinical pyelonephritis occurring during the period of medical management, or, in the surgically treated group, occurring just before corrective operation and the scar appearing within two years after operation.

The majority of renal units in which calyceal clubbing and parenchymal scarring was present had the most severe grades of reflux.

THE PURPOSE of this article, part III of a trilogy, is to review the present status of a group of children with ureterovesical reflux who were observed at Stanford Medical Center and to discuss some general thoughts about the management of these children. Specifically, we will present and discuss the following:

- The incidence and type of infections in a group of children with reflux followed two to ten years.
- The results, infection history and complications of antireflux operations in a group of 61 children.
- The infection history in a group of 73 children with reflux who were treated medically.

Throughout this article the type of reflux to which we are referring is that attributable to a defective ureterovesical junction.[1,2]

This is Part III of a paper in three parts.

From the Department of Surgery, Division of Urology, and the Department of Radiology, Division of Diagnostic Radiology, Stanford University Medical Center, Stanford.

This study was supported in part by Research Grant No. 5 RO1 AI10668, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USPHS.

Dr. Fair is a Recipient of Research Career Development Award No. 5 KO4 AI70107, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USPHS.

Dr. Filly is an Academic Trainee in Diagnostic Radiology, Grant No. GM 1707, National Institute of General Medical Sciences, National Institutes of Health, USPHS.

Reprint requests to: D. E. Govan, MD, Division of Urology, Department of Surgery, Stanford University Medical Center, Stanford, CA 94305.

Material and Methods

Patient categories. This study concerns the investigation, treatment and follow-up of 134 girls with demonstrable ureteral reflux; 61 of them (105 ureters) subsequently had ureteral reimplantation while 73 of them (112 ureters) received medical treatment only (Table 1).

The diagnosis of infection was based in all instances on a positive urine culture, as described in detail previously.[3]

Radiological techniques. All patients had excretory urograms and voiding cystourethrograms.[4] In many instances the excretory urograms were performed elsewhere but, in general, our Radiology Department did the cystourethrograms.

Operation technique. Originally we employed the Hutch modification of his original reimplantation technique, then progressed to the Hutch advancement reimplant;[5] but because of an unacceptably high incidence of failure to correct the reflux, we adopted the Politano-Leadbetter approach.[6] Currently we use a variation of the original Politano-Leadbetter technique in exposing the ureter outside the bladder as well as enucleating it from within. The ureter is re-joined under direct vision, using the Politano-Leadbetter tunneling principle. In second procedures following initial failure or when the ureter had become severely dilated, we cut across the ureter flush with the outside of the bladder and carried out re-anastomosis by the Politano-Leadbetter technique. If the ureter was severely dilated we tapered the distal one-third before reimplanting it.

Treatment and Results

The grade of reflux varied in the two groups; the children who were treated surgically usually were those who had the more severe reflux (Table 2).

Results of Operation

Cure rate. Sixty-one children with 105 refluxing ureters had operation for correction of reflux. The initial operation successfully corrected the reflux in 88 of the 105 ureters (84 percent). Most of the 17 ureters in which reflux persisted after operation had been treated by the Hutch procedure initially. In 14 of the 17, the reflux was corrected by a second operation. The total cure rate, therefore, was 97 percent. Two patients (two ureters) refused further operation and one patient had unilateral nephrectomy. Grade I reflux occurred to a minor degree in two contralateral ureters after operation.

TABLE 1.—*Management of Girls with Ureteral Reflux*

Treatment	*Patients*	*Ureters*
Operation	61	105
No Operation	73	112
TOTALS	134	217

TABLE 2.—*Grade of Ureteral Reflux in Medically Treated and Surgically Treated Children with Urinary Tract Infection*

Grade of Reflux	*Medical Group (Number of Ureters)*	*Surgical Group (Number of Ureters)*
1	44	12
2	60	46
3	8	47
TOTALS	112 (73 patients)	105 (61 patients)

Complications. Ureteral obstruction occurred in eight ureters (six children); in six of these ureters (four children) the obstruction was corrected by ureteral re-anatomosis while in two ureters (two children) there was low grade obstruction which did not require operation. Interestingly, delayed ureteral obstruction occurred in one ureter 30 months following a successful reimplantation. In that case, an excretory urogram appeared normal 12 months after operation. Obstruction in the other seven ureters (five children) was apparent soon after operation. Six ureters became obstructed following the Politano-Leadbetter method of reimplantation. One patient presented with bilateral ureteral obstruction following a Paquin procedure done elsewhere.

Infection results. Urine culture data were studied in all the 134 children with reflux; 61 children had surgical correction of reflux, and 73 were treated medically. We compared the infection data in the two groups of children in reference to the following:

- The infection rate before referral to Stanford.
- The infection rate after corrective operation or medical therapy.
- The incidence of clinical pyelonephritis before referral to Stanford compared with the rate after operation or medical treatment.

Chart 1 indicates the rate and type of infection, measured in infections per patient year, in the two groups of children: (a) before Stanford referral, (b) either following surgical correction of reflux (surgical group) or after continuing medical care

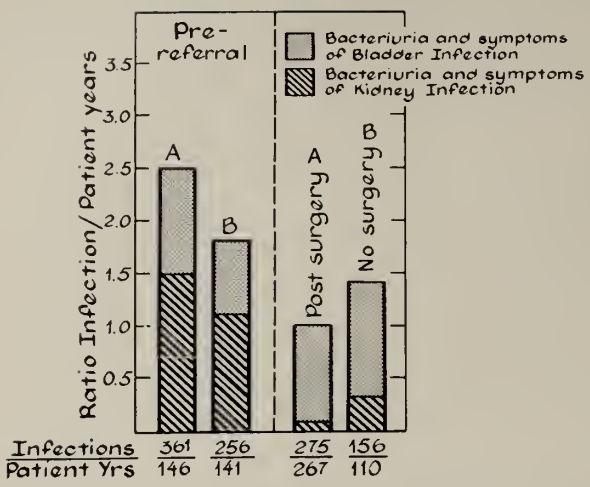

Chart 1.—Illustrates the infections per patient year in the two groups of children pre-referral and post-referral. Group A, reflux and surgically treated group—61 patients. Group B, medically treated group—73 patients.

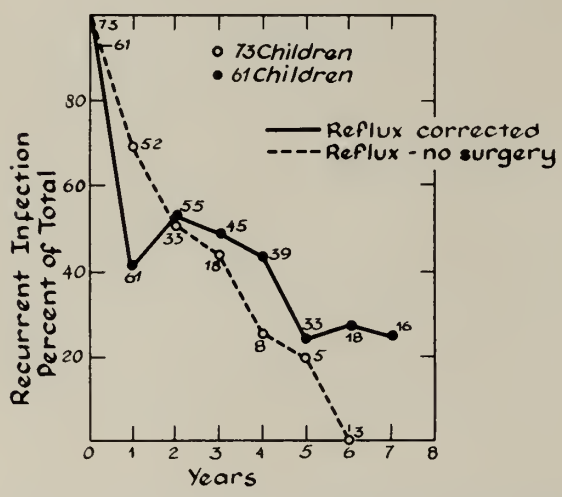

Chart 2.—Annual incidence of infection in two groups of children after surgical correction of reflux (61 children) or after medical follow-up without surgery (73 children).

(medical group). The infection rates were similar in both groups of children before referral. After surgical cure of reflux, the infection rates did not differ significantly. Most importantly, the incidence of clinical pyelonephritis was greater than 50 percent of all infections before referral, but was reduced to 10 percent of the total infections in the surgical group and to less than 20 percent of the infections in the group followed medically.

As shown in Chart 2, of the 73 children with reflux treated medically, 52 were followed for at least one year and 33 for at least two years. Similarly, of the 61 surgically treated children all were followed for at least one year and 55 for two years. The percentage of each follow-up group experiencing recurrent infections in any given year was similar in both groups. Indeed, at a point two years after surgical correction or medical care, more than 50 percent of both the medically and surgically treated children still experienced infections.

Chart 3 gives data on the infections in a child with reflux who experienced her first infection at age four and a half years and who was followed until age 15—eight and a half years after successful left ureteroplasty at age six and a half. This case history clearly indicates the infection incidence and severe morbidity before operation, followed by persistence of recurrent lower urinary tract infections for two and a half years after the procedure. Significantly, there was not a single episode of clinical pyelonephritis after surgical correction of reflux, despite the multiple episodes of bacteriuria which persisted during the initial postoperative period of two and a half years.

Radiological Examinations

The results of the x-ray studies on these children will be presented relative to the following:

- Fate of refluxing renal units treated medically.
- Fate of refluxing renal units treated surgically.
- Relationship of renal clubbing and scarring to grade of ureteral reflux in children treated medically.

Fate of refluxing renal units treated medically. We were able to assess accurately the roentgen features in 110 refluxing renal units at a time not less than one year after the first recorded urinary infection. Forty-eight of these renal units were normal and 62 were clubbed and scarred. The higher the grade of reflux, the higher the observed incidence of clubbing and scarring (Tables 3 and 4).[4]

Multiple roentgen studies of 40 renal units were done over a period of at least two years. Sixteen of the 40 units were initially normal and 14 of these 16 were still normal at the end of the study. Twenty-four of the 40 units were clubbed and scarred when first assessed. In follow-up films nine showed no progression of clubbing and scarring while 15 showed evidence of deterioration. Specific case studies indicated that the infection control in the 15 patients whose kidneys deteriorated further was inadequate. All these patients had multiple episodes of clinical pyelonephritis.

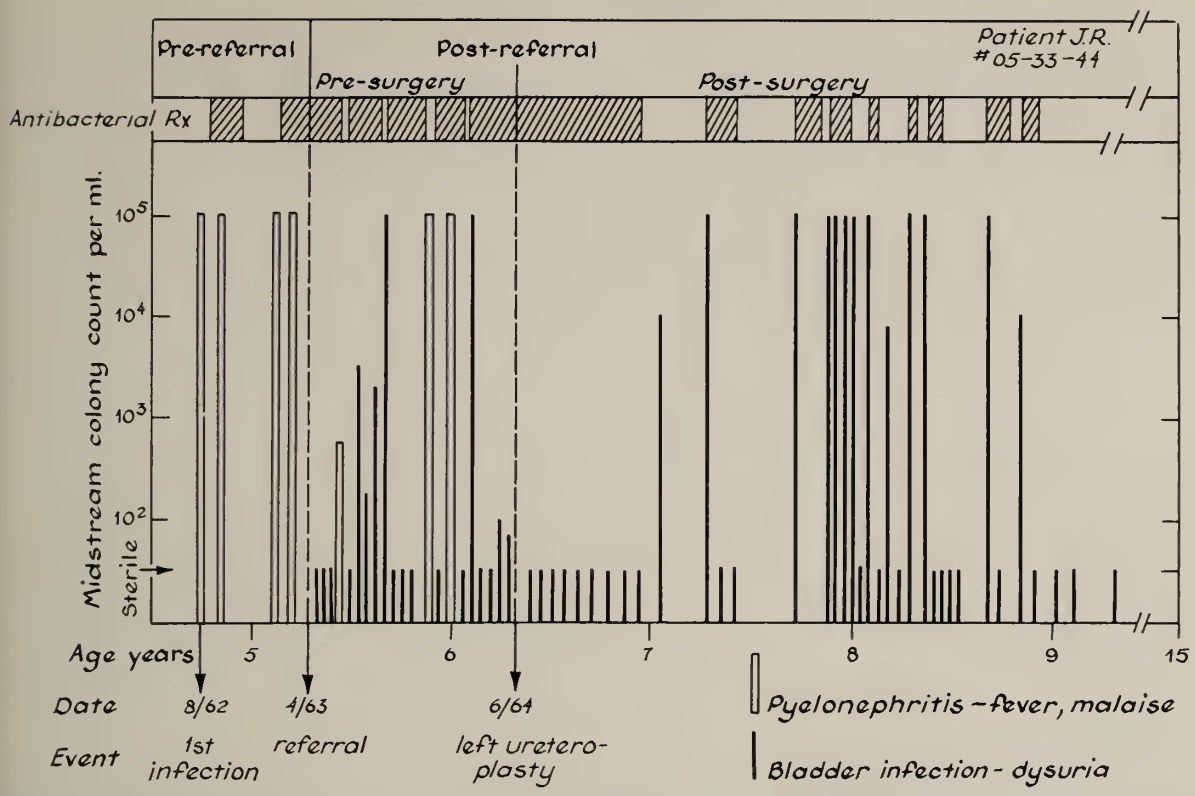

Chart 3.—Documented infection history of a child followed from age 4½ to 15 years, pre-referral, pre-operation and post-operation. Left ureteroplasty was performed at age 6½.

Fate of refluxing renal units treated surgically. Sixty-one children with 105 refluxing renal units had corrective operations (Table 1). We were able to analyze 37 renal units which were followed roentgenologically with multiple examinations for longer than one year postoperatively.[4] Thirteen were normal (35 percent) at time of operation and all remained normal afterward. Twenty-four of the 37 renal units (65 percent) showed clubbing and scarring before operation, and after operation eight showed no progression of renal changes, while 16 deteriorated further. It is important to state that in 13 of these 16 renal units, an acute episode of clinical pyelonephritis occurred just before corrective operation and the scar appeared within two years postoperatively; in three of the 16, a similar pyelonephritic episode occurred after ureteroplasty and the clubbing and scarring progressed within two years after the episode.

Relationship of clubbing and scarring to grade of reflux in children treated medically. In 20 of 26 normal renal units the reflux was grade I, while the reflux was grade III in 36 of 47 renal units with clubbing and scarring (Table 4).[4]

It should be reemphasized that after surgical correction of reflux, no previously normal kidney showed deterioration and that 8 of 24 kidneys which were clubbed and scarred at the time of operation showed no deterioration after operation. Furthermore, all 16 renal units in which clubbing and scarring progressed after operation were in children who had had an episode of clinical pyelonephritis just before the procedure.

Discussion

This article attempts to study the significance of ureteral reflux as it relates to the occurrence of urinary tract infection in girls. Some conclusions can be drawn regarding several pertinent questions.

- *What is the natural history of urinary tract infection in girls with ureteral reflux? And does surgical correction of reflux alter the infection pattern and influence the re-infection rate in these children?*

The results presented in this article and the first article in this series[7] clearly show that the infection rate in children with ureteral reflux who receive only medical therapy is similar to the rate in children without reflux. Before the time of re-

TABLE 3.—*Refluxing Kidneys Treated Medically (From Filly R, Friedland GW, Govan DE, et al[4])*

Renal Morphology	*Right*	*Left*	*Total*
Clubbed and Scarred	33	29	62
Normal	18	30	48
Total Refluxing Kidneys	51	59	110

TABLE 4.—*Relationship Between the Grade of Reflux and Presence or Absence of Clubbing and Scarring (From Filly R, Friedland GW, Govan DE, et al[4])*

STATE OF KIDNEY	0	I	II	III
NORMAL	97	20	17	11
CLUBBED AND SCARRED	3	6	17	36
UNGRADED REFLUXERS (3)				

ferral to our institution, more than 50 percent of infections in children with reflux were associated with fever and flank pain during an infection—quite in contrast to the benign type of clinical infection experienced by children without reflux.[7] In the group with reflux, the severity of infections lessened under good medical management, the incidence of clinical pyelonephritis decreasing to less than 20 percent of all infections. This compares favorably to an incidence of 10 percent in the group of children who had reflux.[7] Winberg et al[8] also found that when infections were well controlled in children with reflux, the incidence of clinical pyelonephritis was similar to that occurring in children who did not have reflux.

Analysis of our 61 children with reflux who had corrective operation and 73 children with reflux who were treated medically points up several facts. First, the incidence of infection in the pre-referral (Chart 1) period was slightly greater in the group of children who ultimately had operation, and the incidence of pyelonephritis was similar in both groups. Second, following either correction of reflux or close medical supervision the incidence of infection decreased. The annual incidence of infection in both groups was still over 50 percent two years after referral (Chart 2). Significantly, however, following anti-reflux operation the incidence of clinical pyelonephritis decreased from 50 percent of infections before to 10 percent of infections after operation. This postoperative incidence of clinical pyelonephritis is identical to that found in a group of children without reflux.[7]

The annual recurrence rate of infection following treatment for both groups of patients is similar (Chart 2). In other words, surgical cure of reflux offers no greater protection from recurrence of infection than medical care alone. In addition, 21 of 61 patients in the surgical group and 11 of 42 patients in the medical group have had no further infection. These differences are not statistically significant.

Because of the similarities between the infection rates in our two groups of children following treatment, we plotted their respective drop-out rate from the infection pool after each successful treatment, against the drop-out rate of the children without reflux who were discussed in the first paper[7] and the theoretical 20 percent extraction rate described by Kunin.[9] Quite significantly the drop-out rates following each successful treatment of an infection were similar for the three groups of children with or without reflux and with or without surgical correction, and paralleled the theoretical 20 percent extraction rate. These data are clearly suggestive that reflux by itself is *not* the influencing factor in the recurrence rate of infection.

In summary of this section, several points need reemphasis: (1) that infections are not totally eradicated following correction of reflux, (2) that the rate of infection in surgically treated and in medically treated patients with reflux is similar, (3) that the incidence of clinical pyelonephritis is similar following surgical or medical treatment, and (4) that the drop-out rate from the infection pool is similar when one compares the surgically treated and the medically treated groups of children who had reflux with the children who did not.

• *Is the persistence of ureteral reflux deleterious to renal morphology and function in the sterile or infected state?*

Our data suggest that reflux, in the presence of infection, is deleterious to renal morphology as judged by renal clubbing and scarring, and that the incidence of clubbing and scarring is highest in association with the higher grades of reflux (Table 4).[4] Unfortunately, our first examination of most of our infected children with reflux did not take place until after the age of two years—few under the age of one year. Hence we did not know the state of ureteral reflux at birth or at the

time of the child's first infection. If it is true that there is a general improvement in the degree of reflux with increasing age of the patient,[10] then the renal units with scarring and low grades of reflux may well have had higher grades of reflux at an earlier age, as suggested by Rolleston et al.[11] Our study also substantiates Rolleston's data that the majority of renal scars occur in the renal units with grade III reflux. Other investigators have found a comparably high incidence of clubbing and scarring in refluxing renal units.[12-14] It is important to state, however, that all of the above observers were studying patients with reflux in the presence of infection. No evidence exists that reflux alone in the absence of infection will lead to functional renal changes.[15,16]

Current Thoughts on Treatment

The general aim of treatment is to sterilize the urine, rid the patient of the annoying symptoms of infection, and prevent renal damage. Our studies strongly suggest that reflux has little influence on the initiation or recurrence of infection because:

- The drop-out rate from the infection pool is similar in children with reflux (surgically or medically treated) and children who do not have reflux.
- The recurrence rates of infection are similar whether correction of reflux was by surgical or medical management.

The incidence of reflux is measurably higher in children with urinary tract infection.[10,17] Numerous investigators have proved, however, that reflux has a tendency to improve or disappear with control of infection, or as the patient get older.[10-13,18-23] Smellie[10] showed that all forms of reflux in children tend to improve in time when the urine is kept sterile.

Additionally, ureteral reflux is rare in infants and older children without urinary tract infection.[24-26] By contrast, among children with infected urine at the time cystogram is done, 45 percent will show reflux.[18]

In a recent communication, Rolleston et al[27] discussed several instances of "intra-renal" reflux in infants under four years of age who had gross ureteral reflux. Renal scarring developed later in the areas of previous intra-renal reflux and, interestingly, scarring did not develop in areas of the same kidney not involved with the intra-renal reflux. These investigators suggested that renal scars might develop in this way in the newborn or infant kidney in the grossly refluxing state even without infection, and conceivably might account for a majority of renal scars apparent in children who first come to the attention of the pediatrician or urologist at age two or three, already with severe renal damage. Has this apparent damage been present since birth and due to primary dysplasia? Has the damage been due to sterile gross reflux and only in areas of intra-renal reflux, or have both possibilities been augmented by the presence of infection? When one combines the above suggestions with the known fact that ureteral reflux seems to improve in time and disappear in a large number of instances,[11,13] it is highly suggestive that when we see a scar in a kidney of a child of three years, with minimal reflux, we may speculate that the reflux was gross at an earlier age, and possibly with an intra-renal component, with or without infections. Our radiological studies[4] have shown that morphologically normal kidneys become clubbed and scarred and that normal areas in otherwise damaged kidneys can become clubbed and scarred. These data suggest that the clubbing and scarring is probably secondary to reflux and infection rather than due to primary renal dysplasia. In experiments in pigs in which he obstructed the urethra and created reflux, Hodson showed focal clubbing and scarring in areas of intra-renal reflux.[28] None of the children in our series, however, had urethral obstruction.

What, then, is the purpose of stopping ureteral reflux? Our studies illustrate that poor infection control in a child with reflux leads to renal clubbing and scarring. Two-thirds of renal units in both the medical and surgical groups that we were able to study with multiple radiological examinations for more than one year showed progressive renal deterioration. In each instance the deterioration seemed to be related to a specific acute clinical pyelonephritic episode months earlier. Moreover, these radiological studies[4] suggested that further scarring of a renal unit took up to 24 months to appear after an infective insult. We would like to be able to say that corrective surgical operation "protected" the renal unit from damage. Our data, however, do not seem to bear this out, unless, of course, we blame the continuing renal deterioration on the infections that occurred before operation. Such seemed to be the case in 13 of 16 renal units in our surgical group in which there was further deterioration after operation.

We feel that the progression of clubbing and

scarring in two-thirds of the renal units in our medically treated group can be blamed on the fact that we used a specific, intermittent ten-day program of drug therapy. Although such treatment effectively eradicated the infection, it did not guarantee protection from the next infection. As a consequence, the child was left "exposed" to possible further renal infection and renal damage.

These data contrast sharply with the absence of progression of renal damage in children (Smellie[10]) for whom continuous antimicrobial therapy was prescribed, generally for the duration of the reflux. In her group of 34 refluxing children treated medically over a period of one to nine years, 26 when first examined had normal kidneys; in 24 of the children the kidneys remained normal and two patients showed slow renal growth. Eight children initially had scarred kidneys and in follow-up two had normal renal growth, two slow growth and four none. Fresh scarring developed in only one neonate following an acute infection.

If reflux is allowed to persist, therefore, the renal unit must be protected from infection. As we shall discuss shortly, we strongly advise initial sterilization of the urinary tract followed by long-term preventive medication for children who have shown a proclivity to frequent bacteriuric episodes.

Current Treatment Regimen

Screening of large numbers of children[17,28,29] has identified those who are bacteriuric with urinary tract abnormalities.[17,29,30] In a recent survey of 8,722 school children five to eleven years of age, Asscher et al[29] found a 1.7 percent incidence of bacteriuria; in this infected group 23 percent had reflux and 17 percent had renal scarring. Such surveys have helped to identify the high incidence of renal disease which seems to exist in the asymptomatic infected population and have alerted clinicians to the need for earlier radiological studies in children who are infected. At the moment it seems important to identify children with urinary tract infection as early as possible. Heale et al[31] indicated that one cannot always predict the presence of infection on symptoms alone. Indeed, Heale found that only 9.1 percent of 789 children presenting at a general pediatric clinic with either specific symptoms such as frequency, dysuria and loin pain, or with nonlocalizing symptoms such as fever, lethargy and abdominal pain, were actually infected. Infection was present in 14.3 percent of children with specific symptoms, but in only 4.4 percent with nonlocalizing symptoms.

Heale[32] subsequently showed that 33 percent of these infected children have either ureteral reflux or a renal scar or both. We should therefore identify the child with symptomatic infection and then investigate further to determine the risk. With that done and the patient treated and evaluated radiologically, one is in a position to outline a program of continuing care.

Treatment of the infection. The presence or absence of reflux does not influence our treatment of an infection. One should treat all infections with a drug most appropriate for the organism involved. Most recurrences of infection are new infections and not a relapse of an old infection.[33] Therefore, we recommend a follow-up urine culture while the child is receiving a ten-day course of antibiotic therapy and again four to seven days after cessation of treatment. Only by this method can we distinguish between relapse and re-infection. If the urine does not become sterile, it may be because of one or more of the following: Use of the wrong antibacterial agent; a new infection; presence of a foreign body such as a calculus; diminished renal function—inadequate to concentrate the antibiotic; or obstruction. In general, however, intelligent use of antimicrobial agents should sterilize the urine.

If a child has frequent infections despite good care, we initially sterilize the urine with specific antimicrobial medication for ten days and then prescribe long-term preventive therapy with nitrofurantoin taken morning and evening or evening only. This regimen is continued for at least six months and then stopped for a trial period as there is always the chance that the patient will drop out of the infected group. If further infection develops, drug therapy is resumed as before. This form of management, used during the latter half of our study, proved to be highly successful, and although our prospective study of results is not yet sufficiently long or involving appropriate numbers of patients, we are encouraged to feel that the control of infections will be as good as reported elsewhere.[13]

Treatment of the reflux. Infection control is paramount in a child with reflux. We adhere to the policy just outlined. If infection cannot be adequately controlled thereby, in our opinion surgical correction is required. Even though our data would suggest a continuing infection pattern in the first two years after operation, in about 50 per-

cent of the children in our series the incidence of clinical pyelonephritis was dramatically reduced.

It is to be hoped that surgical intervention would not be required in a child with grade I or II reflux, for in a majority of cases the reflux will abate with time, as was discussed earlier. In grade III (gross) reflux, one must give consideration to anti-reflux operation even though infection may be quite well controlled, particularly in the younger age group (newborns and infants), on the basis of the discussion already presented.[27]

We strongly oppose the idea of surgical correction of reflux simply because reflux is present. Factors such as age, sex, degree of reflux, infection control, and reliability of the parents of the child must be considered in deciding whether or not to operate. We believe surgical correction of reflux can be justified only on the basis that it will preserve renal function. Good infection control with antimicrobial agents is our recommended treatment; but if control cannot be achieved thereby, then we suggest operative intervention.

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Specialty Conference

Moderator

JAMES S. CLARKE, MD

Discussants

JOHN G. BARTLETT, MD
SYDNEY M. FINEGOLD, MD
SHERWOOD L. GORBACH, MD
SAMUEL E. WILSON, MD

This is one of the monthly Interdepartmental Clinical Case Conferences at the University of California, Los Angeles, School of Medicine, arranged by Dr. William L. Hewitt of the Department of Medicine. Taken from transcriptions, it was prepared by Dr. James S. Clarke, and edited by Mrs. Martha Espada.

Refer to: Clarke JS, Bartlett JG, Finegold SM, et al: Bacteriology of the gut and its clinical implications—Interdepartmental Clinical Case Conference, University of California, Los Angeles, School of Medicine (Specialty Conference). West J Med 121:390-403, Nov 1974

Bacteriology of the Gut and Its Clinical Implications

The bacteriology of the gastrointestinal tract is rapidly changing in laboratory techniques and clinical correlations. The flora is found to be very complex, predominantly anaerobic, and importantly dependent on diet. An etiologic role for colon bacteria in colon cancer is suggested by correlations between epidemiologic data and prevalent dietary patterns and stool culture findings. Cultures from aspiration pneumonia, subphrenic abscess, and other intra-abdominal sepsis all yield anaerobes, and for best results antibiotic therapy should combat them as well as aerobes.

Surgical Considerations

DR. CLARKE:* Welcome to a tour of the darkest reaches of the gastrointestinal tract with swab and culture tube. We shall focus on selected topics of current interest to our faculty and we must here ignore other exciting fields of recent advance in which the bacteria in the bowel play a central role.

It seems valuable to recall that the lumen of the gastrointestinal tract is really outside of the body, part of the "milieu extérieure" as conceived by Claude Bernard. Topologically, it is the hole in the doughnut. Its contents do not achieve the same constancy of osmotic and chemical composition as do the blood plasma and extracellular and intracellular fluids. Moreover, its lower and

*James S. Clarke, MD, Professor of Surgery, UCLA School of Medicine, and Chief of Staff, Sepulveda Veterans Administration Hospital.

From the Department of Surgery, UCLA School of Medicine, and Surgical Service, Wadsworth Veterans Administration Hospital, and Sepulveda Veterans Administration Hospital; and the Department of Medicine, UCLA School of Medicine, and Infectious Disease Sections, Wadsworth Veterans Administration Hospital and Sepulveda Veterans Administration Hospital.

Reprint requests to: J. S. Clarke, MD, Veterans Administration Hospital, Sepulveda, CA 91343.

uppermost reaches are the normal habitat of enormous numbers of bacteria, and in between the bacteria colonize with variable success. It is natural that these bacterial swarms affect in many ways the person on whose surface they live.

The magnitude of these interactions between intestinal bacteria and host becomes understandable when we note the surface area potentially involved. Davenport[1] states: ". . . the area of a normal man's small intestinal mucosa is of the order of 75,000 square centimeters and of his colon 2,500 square centimeters. Microvilli on the intestinal epithelial cells increase their surface area 600 times; therefore, the total absorptive area of the human small intestine is about 4,500 square meters." This is nearly the same surface area as that of our standard football field, which measures 300 feet between goal lines and 160 feet in width. Even ignoring the microvilli, the surface of the small intestine measures 7.5 square meters. Recalling that the external surface of a man 6 feet tall weighing 175 pounds is 2 square meters, it is clear that the intestinal surface is large enough to cause a lot of mischief as well as good.

In this conference our attention will be confined to the normal flora of the gut and the effects of these bacteria when in their usual location (Dr. Finegold), when displaced to other levels of the gastrointestinal tract (Dr. Clarke), and when displaced outside the gut lumen (Drs. Bartlett, Wilson, Gorbach).

There is now ample evidence that both aerobes and anaerobes usually increase in concentration in the small bowel after gastrectomy, vagotomy and drainage, ileostomy, and extensive small bowel resection.[2] The sharp increase in concentration of bacteria in the cecum over the terminal ileum suggests that the ileocecal valve is an important barrier to cephalad colonization of the colonic microflora.[3]

Greenlee and associates[4] performed vagotomy and antrectomy on 20 patients with duodenal ulcer requiring elective surgical operation. They found a consistent and pronounced increase in aerobic and anaerobic organisms of the jejunum, and could find no correlation between bacterial proliferation in the jejunum and gastric secretory output of acid. However, Broido and his colleagues[5] found in dogs that the intestinal bacterial content increased when acid secretion was reduced by gastrectomy or by truncal vagotomy and antrum resection, but not when the vagal fibers to the intestine were cut. From this they concluded that gastric acid is more important than vagal motor factors in regulating the microflora of the small bowel.

Small intestinal overgrowth of bacteria may be clinically benign or may cause one or more manifestations of the surgical malabsorption syndrome.[2] These manifestations include vitamin B_{12} deficiency due to bacterial binding of B_{12}, steatorrhea resulting from deconjugation or dehydroxylation of the bile salts required for micelle formation, diarrhea, protein malnutrition, and impaired absorption of sugars. These can be reversed by appropriate antibiotics taken orally.

The cause of diarrhea after vagotomy is unknown and may be related to the bacterial overgrowth in the jejunum found by Greenlee and associates.[4] Antibiotics have occasionally been found beneficial for continuous diarrhea,[6] but cases are rare and planned trials of antimicrobial agents lacking. Episodic diarrhea, however, occurs with sudden onset and brief duration of attacks, and it is hard to attribute this to vagal denervation of the small bowel, whose motor effect should be continuous. Perhaps newer knowledge of anaerobic bacterial overgrowth and appropriate antibiotics required to suppress it will lead to a solution of this problem.

Hepatic encephalopathy following portacaval shunt is another untoward surgical outcome due to excessive ammonia production by gut bacteria acting on a protein substrate. Peloso, Jacobson, and Silen[7] observed in patients with shunt that there was a worsening of the encephalopathy after a later acid-reducing operation for ulcer disease. Hypochlorhydria resulted in increased ammonia production, probably due to increased bacterial concentrations in the small intestine.

Finally, the value of oral non-absorbable antibiotics for bowel preparation before elective colon operations has been under study for 15 years. Although Gaylor et al[8] found no advantage for oral kanamycin or oral neomycin over a placebo with regard to postoperative infection and stool bacteriology, recent techniques permit quantitative study of anaerobes, which are now recognized to form the major constituent of the feces, and a combination of neomycin and erythromycin base has been shown to suppress both anaerobes and aerobes in the colon.[9] Preliminary studies show a pronounced reduction in incidence of wound infections in patients so prepared as compared with patients having only mechanical bowel cleans-

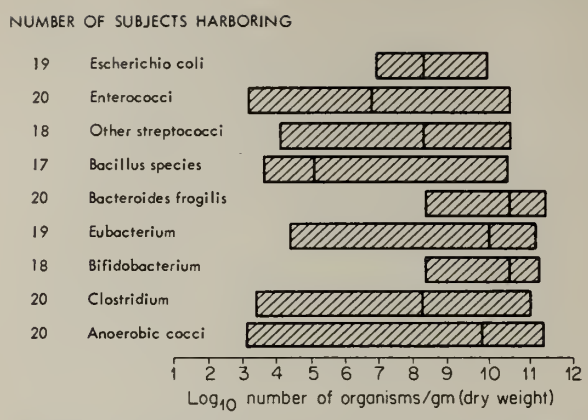

Chart 1.—Predominant human fecal flora: 20 specimens from 18 subjects. The length of the blocks represents the range; the vertical line within the block shows the median count in those subjects who harbored the organism.

ing.[10] Further randomized studies are needed to settle firmly this important question, since the incidence of wound infection in elective colon operations is reported as 10 to 20 percent.

Normal Intestinal Flora: Makeup and Possible Relation to Bowel Cancer

Dr. Finegold:* There are intriguing relationships between diet, intestinal microflora, and bowel cancer. We shall present some data on normal fecal flora, the influence of diet on this flora, and means by which intestinal bacteria may be involved in cancer of the colon.

Inadequacies of Bowel Flora Studies

Our knowledge of the normal colonic flora is far from complete; there are several deficiencies that account for inaccuracies in previously published studies:

- The moisture content of feces is variable and may significantly influence counts based on wet weight of stool. Correcting counts to dry weight avoids this problem.[11]
- Both the water content and bacteria are distributed irregularly through the fecal mass. Accordingly, one must homogenize the entire bowel movement (under anaerobic conditions) before taking an aliquot for culture.[12]
- There has been a failure to use adequate anaerobic technique; anaerobic jars are not adequate for normal flora studies. One must use either an anaerobic chamber (glove-box) or the "roll-tube" procedure, with reduced culture media.
- There has been a failure to use an adequate battery of selective and differential media. Organisms that are not numerically dominant may still be very important as to metabolic and other activities, but may be completely overlooked unless disclosed by selective or differential culture media.
- There has been a failure to provide proper cultural conditions for organisms with special growth requirements. Methane bacteria, for example, require an extremely low Eh (standard oxidation-reduction potential); it is desirable to incorporate hydrogen in the atmosphere.
- There has been a failure to characterize organisms thoroughly. Surprisingly, a number of studies have even failed to distinguish between facultative and obligate anaerobes. Even generic designations may be in error when shortcuts are taken, particularly with anaerobic bacteria.
- The present taxonomic schemes for anaerobes are not adequate and tests for characterizing these organisms are not all dependable. It is often difficult to demonstrate spores, and Gram-positive organisms not uncommonly de-stain and appear Gram-negative.
- There has been a failure to study mucosa-associated organisms.[13]
- There is no reliable information on the day-to-day variation in colonic flora related to minor variations in diet and other factors.

Study of Normal Fecal Flora

Utilizing techniques described in detail elsewhere,[12] we have determined the flora in 20 specimens from 18 adults without gastrointestinal disease. This study was part of a larger one, to be discussed below, to determine the effect of diet on fecal flora. The subjects were all of Japanese descent; they lived in Los Angeles and ate a predominantly Western diet (one Japanese meal daily or less). The data will be presented in greater detail elsewhere at a later date. The present report will summarize the results and give some specific examples of the complexity of the normal fecal flora.

Chart 1 is an overall summation of the predominant fecal microflora. Note that anaerobes are dominant numerically, outnumbering aerobic and facultative forms by almost 3 logs. Bacteroides fragilis and Bifidobacterium are present in the largest numbers, but Eubacterium (commonly

*Sydney M. Finegold, MD, Professor of Medicine, UCLA School of Medicine; and Chief, Infectious Disease Section, Wadsworth Veterans Administration Hospital, Los Angeles. Howard R. Attebery, DDS, and Vera L. Sutter, PhD, collaborated with Dr. Finegold in this section. These studies were supported by a grant from the National Cancer Institute.

TABLE 1.—*Fecal Flora: Facultative Streptococci (20 Specimens)*

Species	*No.**
S. faecalis var. faecalis	15
S. faecalis var. liquefaciens	3
S. faecalis var. zymogenes	3
S. faecium	10
S. durans	1
S. bovis	1
S. equinus ?	2
S. cremoris	4
S. equisimilis	2
S. lactis	2
S. mitis	1
S. salivarius	1
S. sanguis	1
S. species	13

*Number of subjects yielding organism.

TABLE 2.—*Fecal Flora: Eubacterium (20 Specimens)*

Species	*No.**
E. lentum	10
E. aerofaciens	6
E. rectale	4
E. ventriosum	2
E. cylindroides	1
E. limosum	1
E. moniliforme	1
E. tortuosum	1
E. species	19

*Number of subjects yielding organism.

TABLE 3.—*Fecal Flora: Clostridium (20 Specimens)*

Species	*No.**
C. perfringens	12
C. ramosum	11
C. paraputrificum	7
C. glycolicum	6
C. aminovalericum	5
C. innocum	5
C. barkeri	4
C. bifermentans	3
C. oroticum	3
C. indolis	2
C. putrefaciens 'B'	2
C. sporosphaeroides	2
C. cochlearium	1
C. fallax	1
C. inulinum	1
C. irregularis	1
C. malenominatum	1
C. sartagoformum	1
C. species	22

*Number of subjects yielding organism.

TABLE 4.—*Fecal Flora: Anaerobic Cocci (20 Specimens)*

Species	*No.**
Acidaminococcus fermentans	5
Veillonella alcalescens	5
Veillonella parvula	9
Ruminococcus albus	6
Ruminococcus bromii	2
Anaerobic Sarcina	1
Peptostreptococcus intermedius	6
P. productus	5
P. micros	4
Peptostreptococcus species	5
Peptococcus magnus	5
P. prevotii	4
P. asaccharolyticus	1
Peptococcus species	2

*Number of subjects yielding organism.

overlooked in fecal flora studies) and anaerobic cocci are also found in high counts. The special techniques used in this study revealed Bacillus species to be present commonly, though in relatively small numbers.

Table 1 shows the large number of facultative streptococcal species present; despite this, 13 strains did not fit into established species. In the case of Eubacterium (Table 2), there were 19 distinct types not identifiable with any of the recognized species; in the case of Clostridium (Table 3), there were 22 unidentifiable groups despite the presence of 18 recognized species. The frequency with which C. ramosum may be found has not been generally appreciated. C. paraputrificum may be of special significance in relation to bowel cancer, inasmuch as this organism has been shown to carry out certain modifications of bile acids that might represent transformation of these compounds toward carcinogenic agents.[14,15] Table 4 shows that a variety of genera, as well as of species, of anaerobic cocci were recovered.

In order to determine to some extent the degree of variability that might be encountered in specimens taken at different times from the same person, duplicate specimens were run on seven subjects with an interval of two weeks to 19 weeks between specimens. The results are presented in Table 5. When organisms were analyzed primarily in broad groups, differences between the two specimens were relatively minor. Problems with the lactobacilli and with Eubacterium lentum were related to the lack of effective selective or differential media for these organisms, which are not numerically dominant. The results were also inconstant with the methane bacteria, perhaps relating to the fact that these organisms are extremely difficult to grow. When species were compared in duplicate specimens, there was quite

a bit of variation with some of the anaerobes; this very likely reflects problems in both the classification and characterization of these organisms.

Effect of Diet on Fecal Flora

The flora in 20 specimens from the above-discussed 18 persons eating a Western diet was compared with flora in 20 specimens from 15 subjects of Japanese descent also living in Los Angeles but eating a predominantly traditional diet (two Japanese meals per day). The data with regard to differences between the two groups are shown in Table 6. Aerobic counts were higher on the Japanese diet, whereas anaerobic counts and ratio of anaerobes to aerobes were somewhat higher on the Western diet. Despite the latter finding, certain fastidious anaerobes, such as extremely oxygen-sensitive (EOS) forms and spirochetes, were more prevalent on the Japanese diet. Certain Gram-positive nonsporeforming anaerobic bacilli (Eubacterium) were more prevalent on the traditional diet, whereas others (Bifidobacterium) were so on the American diet. Similar findings were also noted with different groups of anaerobic cocci. Clostridium paraputrificum was found somewhat more frequently in subjects on the Western diet. The differences noted have not yet been analyzed statistically.

TABLE 5.—*Fecal Flora: Comparison of Duplicate Specimens (7 Subjects)*

Group	*A**	*B†*	*C‡*
Coliforms	6	..	1
Streptococci, Group D	6	1	..
Streptococci, other	4	2	1
Lactobacilli	4	3	..
Bacteroides fragilis	7	..	..
Fusobacterium	7	..	..
Eubacterium lentum	1	5	1
Bifidobacterium adolescentis	7	..	..
Bifidobacterium infantis	5	2	..
Peptostreptococcus	6	1	..
Veillonella	6	1	..
Methane bacteria (5 subjects)	3	2	..

*No difference between specimens.
†Present in one, absent in other.
‡Present in both, but 4 log or greater difference.

Relation of Bowel Flora to Colon Cancer

The incidence of colon cancer is generally much higher in developed countries. Japan is a notable exception—a highly developed country with a low incidence of bowel cancer. When Japanese migrate to the United States, however, their incidence of bowel cancer goes up considerably unless they maintain their traditional diet.[16-18] This, of course, indicates that diet plays an important role in bowel cancer. Studies such as that presented herein and others show that diet may influence the bowel flora significantly. The elements of the diet that are common to countries with a high incidence of colon cancer and that are not seen in areas with low bowel cancer rates are the high fat and animal protein content.

There are many reasons to consider that bile acids may be very important intermediaries in bowel cancer.[19] Certain bile acids and bile acid derivatives such as deoxycholic acid and apocholic acid are carcinogenic. A very potent carcinogen, methylcholanthrene, may be produced from bile acids by a series of reactions that can be carried out by bacteria. (However, it is not established

TABLE 6.—*Fecal Flora: Differences Related to Diet (20 Specimens for Each Diet Group)*

Species	*Japanese Diet*	*Western Diet*
Aerobic counts	Higher	...
Presence of EOS anaerobes	15/20	5/20
Spirochetes present	3/20	0/20
Lactobacillus	Greater prevalence and variety	...
Streptococcus bovis	Higher count	...
Bacteroides putredinis	0/20	2/20
Bacteroides pneumosintes	2/20	0/20
Unidentifiable bacteroides	More common	...
Eubacterium contortum	5/20	0/20
Eubacterium lentum	16/20	10/20
Bifidobacterium	...	More prevalent
Peptostreptococcus	Much more prevalent	...
Megasphaera	2/20	0/20
Other anaerobic cocci	...	More prevalent
Clostridium paraputrificum	5/20	7/20
Unidentifiable clostridia species	Much more common	...

EOS = extremely oxygen-sensitive.

TABLE 7.—*Predisposing Causes for Aspiration (70 Cases)*

Compromised consciousness	
Alcoholism	23
Cerebrovascular accident	13
Seizure disorder	9
General anesthesia	9
Drug ingestion	8
Miscellaneous	5
Dysphagia	
Neurologic disorder	7
Esophageal stricture	2

that these can be carried out by intestinal microorganisms.) It is known, nevertheless, that intestinal bacteria, particularly anaerobes, are capable of modifying bile acids in a variety of ways, including dehydroxylation, which is responsible for the production of the secondary bile acid deoxycholate.

It has also been shown that vegetarians have a lesser amount of bile acids in their feces than people on a mixed diet, and that fewer of the anaerobes from the former group are capable of dehydroxylating primary bile acids.[20]

In addition to direct production of a carcinogen by bacteria, other ways in which intestinal bacteria might lead to malignant change include modification of the host response to carcinogens or modification of the host response to cancer.[19]

The Bacteriology of Pulmonary Infections Following Aspiration

Dr. Bartlett:* Aspiration pneumonia encompasses a variety of pulmonary conditions with diverse manifestations. Often the clinical features suggest infection, but the pathogens in such cases have not been adequately studied because of the failure of previous investigators to obtain reliable specimens or to utilize optimal laboratory methods.

We have been conducting a prospective study of pulmonary infections following suspected aspiration during the past four years. The bacteriological findings in 70 patients are the subject of this report. A detailed analysis of 54 of these cases has been previously reported.[21]

The criteria for inclusion in this study were (1) observed aspiration or a predisposition to aspirate due to altered consciousness or dysphagia, (2) roentgenographic evidence of an inflammatory response in a dependent pulmonary segment, and (3) availability of a reliable specimen for culture before antimicrobial therapy. Culture sources utilized were percutaneous transtracheal aspirates (63 cases), empyema fluid (eight cases), or positive blood culture (four cases). (Two of these specimen sources were utilized in three cases.) Expectorated sputum cultures were not considered acceptable, as these specimens are not valid for anaerobic culture and are often unreliable with aerobic culture.[22-24]

Percutaneous transtracheal aspirates and pleural fluid specimens were processed immediately or were held in tubes containing oxygen-free gas. In all instances the duration of air exposure from the time of collection until incubation was limited to 20 minutes and seldom exceeded 10 minutes. Media routinely used were: eosin-methylene-blue agar for incubation in air; blood agar and peptic digest of blood (Fildes' extract) agar for incubation in 5 percent CO_2; Brucella base-menadione-blood agar and a selective agar (kanamycin-vancomycin laked-blood agar or neomycin-blood agar) for incubation in anaerobic GasPak jars; and pre-reduced, anaerobically sterilized, chopped-meat glucose broth inoculated under oxygen-free CO_2. Plates incubated in air and 5 percent CO_2 were read at 24 hours. GasPak jars were not opened until after 48 hours' incubation and were held a total of seven days. Chopped-meat glucose broth was subcultured at 72 hours and at three weeks. Aerobic and facultative isolates were identified by conventional schema. Anaerobic isolates were identified by criteria listed in the Anaerobic Laboratory Manual of the Virginia Polytechnic Institute and State University.[25]

Table 7 summarizes the associated conditions that predisposed these patients to aspiration. Most of the patients had altered consciousness as a result of alcoholism, cerebral vascular accident, seizure disorder, general anesthesia, or drug ingestion. Less common conditions causing compromised consciousness included cardiogenic shock, smoke inhalation, hepatic coma, encephalitis, and Korsakoff's syndrome. Nine patients had dysphagia as a result of a neurological disorder not associated with compromised consciousness or due to an esophageal stricture. (Six patients had two of the conditions listed.)

The types of pathologic processes according to chest x-ray appearance were pneumonitis (38 cases), solitary pulmonary abscess (20 cases) or

*John G. Bartlett, MD, Assistant Professor of Medicine, UCLA School of Medicine, and Infectious Disease Section, Veterans Administration Hospital, Sepulveda, California.

multiple small pulmonary abscesses (12 cases). There was associated empyema in eight cases.

Localization of the pulmonary infection indicated the following sites were principally involved:

Site	*Number*
Right upper lobe, posterior segment	16
Right lower lobe, superior segment	9
Right lower lobe, basilar segments	13
Left upper lobe, posterior apical segment	4
Left lower lobe, superior segment	5
Left lower lobe, basilar segments	8
Bilateral lower lobes, basilar segments	15

Bacteriological results are summarized in Tables 8 and 9. In 52 cases (45 percent) anaerobic bacteria were the only pathogens isolated, nine patients (13 percent) had an exclusively aerobic flora, while 29 (41 percent) had a combination of both aerobes and anaerobes. In 16 cases a single organism was recovered in pure culture. The remaining 54 patients had multiple isolates with an average of 3.3 kinds of bacteria per case; this included 2.3 anaerobes and 1 aerobe. Thus, the flora in most of these patients was complex, a finding in contrast to our experience with other types of bacterial pneumonitis in which a single organism (usually the pneumococcus) is recovered in pure culture.

As to specific microorganisms (Table 9), the predominant anaerobic isolates were Bacteroides melaninogenicus, Fusobacterium nucleatum, and anaerobic Gram-positive cocci. Bacteroides fragilis was found in 10 instances; the recovery of this organism may have important therapeutic implications because B. fragilis is usually resistant to commonly used antibiotics such as penicillins, cephalosporins, and tetracycline.

The predominant aerobic and facultative bacteria were Diplococcus pneumoniae, Staphylococcus aureus, enteric Gram-negative bacilli, and pseudomonads. These organisms were seldom recovered in pure culture and in all but nine cases anaerobic pathogens were present concurrently.

Although bacteriological patterns were sought, consistent associations were generally not apparent. That is, the nature of the isolates was similar regardless of the roentgenographic appearance, predisposing condition, or eventual outcome. It was noted, however, that the 32 cases of aspiration pneumonia that occurred while the patient was in hospital were more likely to involve mixtures of aerobes and anaerobes (Table 8), in contrast to the 38 cases of community-acquired infections, which usually yielded only anaerobes. This finding was particularly apparent with the enteric Gram-negative bacilli and pseudomonads: 16 of the 22 patients with infections involving these organisms acquired their disease while in hospital.

The therapeutic implications of our findings indicate that, as with other types of infections, antibiotic selection is best determined by the results of proper processing of a reliable specimen. Expectorated sputum should not be used in these cases, as these specimens are not valid for anaerobic culture and are frequently unreliable with aerobic culture. When empirical therapy is necessary for infections following aspiration, agents

TABLE 8.—*Types of Bacteria Recovered in Aspiration Pneumonia*

Origin	*Cases*	*Anaerobes only*	*Aerobes only*	*Anaerobes and Aerobes*
Hospital-acquired	32	7	6	19
Community-acquired	38	25	3	10
TOTALS	70	32	9	29

TABLE 9.—*Bacteriology of Aspiration Pneumonia (70 Cases)*

Anaerobic Gram-negative bacilli		
Bacteroides melaninogenicus	27	(1)*
B. fragilis	10	(1)
B. oralis	9	
B. corrodens	2	
B. pneumosintes	1	
Fusobacterium nucleatum	19	
F. necrophorum	1	
Unidentified	4	(1)
Anaerobic cocci		
Peptostreptococcus	23	(5)
Peptococcus	11	(1)
Microaerophilic streptococcus	9	(1)
Veillonella	4	
Anaerobic Gram-positive bacilli		
Eubacteria	6	
Propionibacteria	6	
Bifidobacteria	2	
Clostridia	2	
Aerobic Gram-positive cocci		
Diplococcus pneumoniae	11	(2)
Staphylococcus aureus	11	(2)
Enterococcus	3	
Group A β-hemolytic streptococci	2	
Aerobic Gram-negative bacilli		
Klebsiella sp.	8	(2)
Pseudomonas aeruginosa	7	
Escherichia coli	6	
Enterobacter cloacae	4	
Hemophilus influenzae	2	
Citrobacter freundi	1	
Pseudomonas maltophilia	1	

*In parentheses: number recovered in pure culture.

that are active against anaerobes should be included, since these organisms were incriminated in 87 percent of the cases reviewed.

Changing Patterns in Diagnosis and Treatment of Subphrenic Abscess

DR. WILSON:* In the early 1900's, the likelihood of subphrenic abscess following appendectomy was approximately 0.9 to 1.5 percent.[26] Although the frequency of this postoperative complication has decreased to the present incidence of 0.3 to 0.4 percent, subphrenic abscess warrants reconsideration for several reasons. Almost half of all intra-abdominal abscesses are located in the subphrenic area. The alarming mortality of 20 to 40 percent appears relatively constant despite the general availability of skilled anesthesia, the use of antibiotics, and improved knowledge of surgical metabolic problems. This mortality is related in part to difficulties in diagnosis, with resultant delay of surgical treatment for weeks. The subphrenic abscess has not been a static syndrome, and perhaps its clinical vicissitudes account for the difficulty in prompt diagnosis and treatment.

Originally, perforated peptic ulcer and appendicitis accounted for the majority of subphrenic abscesses. Improved surgical treatment of these conditions has reduced their etiologic importance, and now most subphrenic abscesses occur as postoperative complications of elective duodenal ulcer and biliary tract procedures. Table 10 indicates the related procedures in a series of 88 subphrenic abscesses encountered between 1958 and 1971 at the UCLA Medical Center and the Veterans Administration Wadsworth Hospital Center. Gastric and biliary operations together accounted for almost 60 percent of the subphrenic abscesses. Surgical operation for disease of the large bowel, the third most common cause, was responsible for 15 percent of subphrenic infections.

The topography of the subphrenic area, long a matter of anatomical confusion, was clarified by Boyd's classical article in 1966.[27] He established that the coronary ligament has a dorsal attachment, with a large suprahepatic space on each side. Therefore, the area between the diaphragm and the transverse colon is divided into four subphrenic spaces: right and left subdiaphragmatic, subhepatic, and lesser sac. Previous anatomical descriptions were often based on pathological findings, so that the spaces described were actually defined by pyogenic membranes.

TABLE 10.—*Subphrenic Abscess: Related Surgical Procedures UCLA-Wadsworth, 88 Patients*

Surgical Procedure	*No.*	*Percent*
Stomach	27	31
Biliary tract	25	28
Colon	15	17
Appendix	7	8
Other (Spleen, Pancreas, Trauma)	14	16

TABLE 11.—*Subphrenic Abscess: Location*

	1909		*1942*		*1973*	
Site	*%*	*No.*	*%*	*No.*	*%*	*No.*
Right subphrenic	56	469	50	50	30	26
Left subphrenic	37	296	10	10	45	40
Subhepatic	..	..	35	35	8	7
Combined	3.5	28	6	6	17	15

Reports: 1909, Piquand[28]; 1942, Hochberg[29]; 1973, UCLA-VA.

In the UCLA-Wadsworth group of 88 patients, the abscesses were mainly localized to the right and left subdiaphragmatic areas, with the subhepatic and lesser sac spaces involved less frequently (Table 11). Early reports[28,29] on subphrenic abscess indicate that the right subdiaphragmatic space was by far the commonest location. Appendicitis is now less frequently associated with abscess formation, and the trend is for the left side of the abdomen to be more frequently involved. In most series, infection of the right subphrenic space is still more common, probably due to localization of infection following cholecystectomy and appendectomy to this area. Of greater significance is the large percentage of multiple space involvement necessitating a transabdominal approach for drainage.

The bacteriology of the subphrenic abscess, although still quite similar to that of the preantibiotic era, has shown some changes. Multiple flora were encountered in 36 percent of the 67 patients who had adequate bacteriologic study, in contrast with the pure cultures usually found before general antibiotic use. The three predominant organisms are still E. coli, Streptococcus and Staphylococcus (Table 12), which was also the case in Ochsner and DeBakey's 1938 study.[30] The frequency of Streptococcus has declined somewhat, however, to be replaced by Gram-negative organisms such as Klebsiella-Aerobacter and Proteus. Early antibiotic administration has apparently reduced the number of positive blood cultures, and secondary complications such as

*Samuel E. Wilson, MD, Assistant Professor of Surgery, UCLA School of Medicine, and Chief, General Surgery Section, Surgical Service, Veterans Administration Wadsworth Hospital Center, Los Angeles.

TABLE 12.—*Subphrenic Abscess: Bacteriology UCLA-VA Study, 65 Patients*

Organism	*No.*	*Percent*
Escherichia coli	39	60
Streptococcus	32	49
Staphylococcus	20	31
Klebsiella-Aerobacter	11	17
Proteus	7	11
Pseudomonas	5	8

TABLE 13.—*Subphrenic Abscess: Mortality*

Year	*Study*	*Number Patients*	*Percent Mortality*
1908	Barnard[32]	76	47
1938	Ochsner and DeBakey[30]	3,608	53
1955	Harley[34]	212	39
1962	Dineen and McSherry[33]	63	43
1973	UCLA-VA	88	33

diaphragmatic perforation, empyema, and free peritoneal rupture are now exceedingly rare.

The widespread use of antibiotics accounts for the slow, insidious nature in which the subphrenic abscess may present today. In a typical case, two weeks after a surgical procedure the patient complains of malaise, mild abdominal pain, and low-grade fever; on examination there may be tenderness along the anterior costal margin, and leukocytosis is present in 90 percent of patients. Carter and Brewer in 1964[31] emphasized the thoraco-abdominal nature of the subphrenic abscess, pointing out that findings related to the chest predominated in 44 percent of their patients. Roentgenograms of the chest may disclose an area of pneumonitis, basal atelectasis, elevation of the diaphragm, or perhaps a small pleural effusion. Combined liver-lung scan is useful in delineating a "cold area" caused by depression of the superior surface of the liver when there is a right subdiaphragmatic abscess.

The mortality from subphrenic abscess has remained surprisingly high (Table 13) despite the promise of extraperitoneal drainage and newer broad-spectrum antibiotics. The prognosis is particularly severe in patients with multiple abscesses, 65 percent of whom may have a fatal outcome. Underlying disease processes (such as malignant disease) and secondary complications (including generalized peritonitis, sepsis, or intestinal fistulization) are associated with poor prognosis. Missed diagnosis and a prolonged interval before surgical drainage are related to increased mortality rates. The mean stay in hospital of 54 days for surviving patients at the UCLA Medical Center reflects the extensive morbidity of the disease.

An extraperitoneal approach has been advocated since 1939 as the optimal route, as avoiding contamination of the intraperitoneal cavity was presumed to lower mortality. In a critical analysis of this traditional view, Halasz[35] recently emphasized that multiple synchronous abscesses occur in as many as 25 percent of patients, and that this group has the highest mortality. The major cause of death was a missed second or even third abscess. In a prospective series of patients, a lower mortality was achieved utilizing a midline transperitoneal approach, careful abdominal exploration, and dependent drainage through the flanks with large-bore sump tubes.

Normal Bowel Flora and Intra-Abdominal Sepsis

DR. GORBACH:* The lower gastrointestinal tract harbors a high density of microorganisms. Anaerobic species—particularly bacteroides, clostridia, and peptostreptococci—are present in total concentration of 10^{11} per gram, outnumbering coliform species by approximately three logs.[36-42] It follows therefore that intra-abdominal sepsis, especially when associated with contamination by bowel contents, will have a mixed flora comprising both aerobic and anaerobic microorganisms. Although this formulation is eminently logical, recent studies[43-51] of abdominal infections do not consider anaerobic bacteria important, assigning this group of microorganisms to curiosities associated with rare diseases. With the advent of sophisticated techniques to culture anaerobes in clinical material,[52,53] this view may have to be revised.

We have studied 46 patients who were referred to the Infectious Disease Service for intra-abdominal sepsis. Included were 32 patients with intra-abdominal abscess, ten with generalized peritonitis, and four with miscellaneous infections such as retroperitoneal and prostatic abscesses and an infected aortic graft. All of these patients had had abdominal surgical operations and had received antibiotics postoperatively for signs of infection. The Infectious Disease consultation was requested because of persisting sepsis.

Predisposing conditions included trauma, generally due to gunshot or knife injuries (22 patients); carcinoma of the colon, pancreas, or kidney (17 patients); intestinal surgical therapy

*Sherwood L. Gorbach, MD, Professor of Medicine and Microbiology, UCLA School of Medicine, and Chief, Infectious Disease Service, Veterans Administration Hospital, Sepulveda, California.

with postoperative complications (seven patients); perforated appendix (four patients); cirrhosis with spontaneous peritonitis (three patients); and peritoneal dialysis with intestinal perforation (three patients).

Bacteriologic cultures were obtained from 43 specimens of purulent drainage collected directly from surgical incisions. The other three patients had positive blood cultures, but no abdominal sites were available for culture. Anaerobic techniques utilized oxygen-free conditions and prereduced culture media; these methods have been shown to give a high yield of fastidious anaerobes from clinical material.[36,54] The flora recovered from 33 of the 43 specimens of purulent material contained a mixture of aerobic and anaerobic bacteria; an exclusively anaerobic flora was present in seven patients; three had only aerobic or facultative bacteria. Thus, anaerobic bacteria could be cultured from 40 of 43 wounds (93 percent) in patients with severe intra-abdominal sepsis.

The cultivable flora from intra-abdominal sites was characterized by several isolates of different bacterial species. There was an average of five microorganisms cultured from a single specimen, with a range of one to thirteen isolates; this included an average of two aerobes and three anaerobes. It can be appreciated that intra-abdominal sepsis represents a complex microbial flora with multiple types of bacteria.

The aerobic and facultative microorganisms (Table 14) were similar to those reported in other series. Of note is the low incidence of S. aureus, a reflection of the current era of hospital epidemiology. Gram-negative enteric organisms such as proteus, klebsiella, E. coli, pseudomonas and enterobacter are now isolated with greater frequency.

A large variety of anaerobic species was cultured from these intra-abdominal infections (Table 15). Bacteroides was the most frequent isolate, recovered on 36 occasions; the species Bacteroides fragilis represented 28 of these strains, and other species were present less commonly. Fusobacteria were isolated on six occasions. Clostridial species were isolated nearly as frequently as bacteroides (31 specimens); these included 13 known species and 10 strains that could not be further identified. It is interesting to note that Clostridium perfringens was isolated in only three patients, and was seen as frequently as Clostridium ramosum. None of the patients associated with histotoxic strains of clostridia had clinical signs of gas gangrene. Anaerobic cocci were present in 14 patients, with a preponderance of peptostreptococci. Peptococci were isolated in three patients, and veillonella in one. Gram-positive, nonsporing rods were recovered in 16 pa-

TABLE 14.—*Anaerobic and Facultative Microorganisms Isolated from 46 Intra-abdominal Infections*

Organism	*No.*
Escherichia coli	28
Staphylococcus epidermidis	15
Proteus	10
Klebsiella	9
Pseudomonas	8
Enterobacter	8
Candida	4
Streptococcus	3
Enterococcus	2
Staphylococcus aureus	1

TABLE 15.—*Anaerobic Microorganisms Isolated from 46 Intra-abdominal Wounds*

Organism	*No.*
Gram-negative nonsporing rods	
Bacteroides	36
B. fragilis (28)	
B. melaninogenicus (4)	
B. clostridiiformis (2)	
B. biacutus (1)	
B. species (1)	
Fusobacterium	6
F. varium (1)	
F. necrophorum (1)	
F. species (4)	
Cocci	
Peptostreptococci	11
Peptococcus	3
Pc. magnus (2)	
Pc. prevotii (1)	
Veillonella	1
Clostridia	31
C. ramosum (3)	
C. perfringens (3)	
C. butyricum (2)	
C. bifermentans (2)	
C. sporogenes (2)	
C. innocuum (2)	
C. sordellii (1)	
C. fallax (1)	
C. beijerinckii (1)	
C. barati (1)	
C. difficile (1)	
C. ghoni (1)	
C. sphenoides (1)	
C. species (10)	
Gram-positive nonsporing rods	
Eubacterium	11
E. lentum (6)	
E. filamentosum (2)	
E. multiforme (1)	
E. limosum (1)	
E. species (1)	
Propionibacterium	2
Lactobacillus catenaforme	2
Bifidobacterium	1

TABLE 16. *Microorganisms in 13 Cases of Septicemia Associated with Intra-abdominal Infections**

Organism	*No.*
Bacteroides fragilis	8
Bacteroides melaninogenicus	1
Clostridium perfringens	2
Clostridium tertium	1
Clostridium difficile	1
Fusobacterium fusoforme	1
Klebsiella	2

*Two patients had B. fragilis and Klebsiella; one patient had two strains of Clostridia.

tients. We believe at present that Eubacterium species are nonpathogens; all of these isolates were present in mixed cultures, usually associated with bacteroides.

To summarize: of the types of anaerobes isolated from cases of intra-abdominal sepsis, three groups of organisms were most frequently involved: Bacteroides fragilis, clostridia, and anaerobic streptococci, especially the peptostreptococci. This pathogenic triumvirate has been cultured repeatedly from patients with intra-abdominal infections.

Positive blood cultures were present in 13 of the 46 patients (28 percent). Eleven patients had exclusively anaerobic growth and two had mixed aerobic and anaerobic growth, but there were none with exclusively aerobic organisms. As in the cultures from pus, Bacteroides fragilis was the predominant organism isolated in the bloodstream, found in eight of the thirteen positive cases (Table 16). Two of these patients had a mixed culture of Bacteroides fragilis and klebsiella; clostridia septicemia was noted in three patients; one patient had two strains of clostridia—C. perfringens and C. tertium—in his blood on repeated occasions; Bacteroides melaninogenicus and fusobacteria were present in one patient each.

Previous studies[43-51] of the bacteriologic features of intra-abdominal sepsis have suggested that the offending bacteria were usually aerobic, enteric bacilli. Anaerobes were considered a curiosity that caused only special types of infections such as gas gangrene, burrowing ulcers, or necrotizing fasciitis.

The application of rigorous techniques for culturing anaerobes in clinical material has produced a new understanding of the microflora of intra-abdominal infections. It appears that the flora is often a complex ecosystem. There are on the average five bacteria in each infection, and we have seen patients with as many as 13 distinct microbial species in a single infected site.

The recognition of anaerobes in abdominal wounds has important implications for antimicrobial therapy. On the basis of *in vitro* testing, it would appear that certain drugs are acceptable for treatment of mixed aerobic and anaerobic infections, whereas other antibiotics are unacceptable.[55-57] For example, when considering Bacteroides fragilis, the most frequent isolate in intra-abdominal sepsis, the acceptable group of antibiotics includes chloramphenicol and clindamycin as the most satsfactory agents.[58-63] On the other hand, there is good evidence that penicillins, cephalosporins, and aminoglycoside antibiotics have relatively poor activity against B. fragilis. New informaton on antibiotic susceptibilities, combined with the data on anaerobic bacteriology in intra-abdominal infections, should cause a reassessment of the use of antibiotics in such conditions.[64-67]

Discussion

DR. HEWITT:* Dr. Gorbach, actually you are showing the isolation of many clostridia in these patients. I wonder what you think the role of these organisms may be in patients who really don't show gas in tissue and other signs that are ordinarily associated with clostridia infections.

DR. GORBACH: Gas gangrene is a rare event in civilian hospital practice, even when many histotoxic strains of clostridia can be cultured from open wounds. In other studies of penetrating intra-abdominal trauma we showed that the flora of healing wounds, including clostridia, was essentially the same as that of infected wounds. Thus, the decision concerning the presence of infection was clinical, and not based on the bacteriologic findings. This is especially pertinent to the study of clostridia. The most common setting of positive cultures for this organism is simple contamination. We could speculate on the conditions that transform contamination into pathogenic circumstances, such as necrotic tissue, low oxidation-reduction potential, low pH, and calcium. The important lesson for the clinician is not to panic in the face of a positive clostridial culture. More often than not, the organism is either a contaminant or part of the complex flora of an abscess,

*William L. Hewitt, MD, Department of Medicine, UCLA School of Medicine.

rather than producing the classic picture of gas gangrene and myonecrosis.

DR. CLARKE: Dr. Gorbach, would you comment on the role of sensitivities when you have 20 different bacteria and you are trying to pick an antibiotic?

DR. GORBACH: I will have to take the Fifth Amendment on that question. In fact, it becomes an impossible task for the laboratory to do antibiotic sensitivity determinations on each isolate in the complex flora of an abscess, and an intolerable task for the clinician at the bedside to interpret the data. In my view, our current priorities are misplaced. Rather than the relentless pursuit of individual sensitivity tests, we should be asking basic biologic questions. It is far more pertinent to understand which organism(s) is the pathogen, which is the symbiont, and which is the harmless commensal. It is quite obvious that treating commensals will neither help the patient nor cure the disease. Until these basic questions are answered, we have taken the empirical approach of using two broad-spectrum drugs for mixed infections associated with intestinal perforation. One agent is an aminoglycoside such as gentamicin or kanamycin to control the facultative Gram-negative bacilli; the other agent is selected to control anaerobic bacteria, the current choice being either clindamycin or chloramphenicol. We have now treated more than 50 patients with this empiric regimen, and the results have thus far been satisfying.

DR. CLARKE: What are the chances that anaerobes will develop resistance to the two drugs that you have now? Do you have other drugs waiting in the wings?

DR. GORBACH: It is not a certainty that resistance will develop in microorganisms to all antimicrobials. For example, we have not seen significant resistance to penicillin in Streptococcus pyogenes or Diplococcus pneumoniae, even though this antibiotic has been used in treating disease caused by these organisms for over 30 years. Similarly, we have not noted significant resistance of Bacteroides fragilis to chloramphenicol despite the availability of this agent since 1948. With regard to newer drugs such as clindamycin, we will have to adopt a "watchful waiting" approach. It may require five years of observation with standardized techniques in order to determine whether organisms are progressively developing resistance. We should be aware that it is not inevitable that organisms develop resistance to antibiotics the way we are accustomed to seeing in staphylococcus or pseudomonas.

Question: Dr. Gorbach, do you think the 33 percent mortality that Dr. Wilson mentioned in subphrenic abscess is going to be considerably reduced by the advent of clindamycin? Why is that mortality occurring? Is it because the surgical operation is inadequate or is it because the infection is not well controlled?

DR. GORBACH: This is a difficult question, as there are many factors that relate to surgical mortality. The patients described in our series were often healthy young men who incurred gunshot or knife wounds to the abdomen. On the other hand, Dr. Wilson's patients were generally older persons who had rather low resistance. Thus, the two groups are not readily comparable. I would emphasize that expertise in anaerobic bacteriology and the use of appropriate drugs in these settings may improve the outcome for such patients. This is not to deny the primary importance of adequate surgical drainage of closed-space infections, but we must recognize that proper use of effective antibiotics is a significant adjunct. Some patients will continue to have suppurative infections, bacteremia, and even insidious extension of the process if they are treated with ineffective drugs. Hence, all three elements are important in the cure of chronic intra-abdominal abscesses—good host defenses, judicious surgical drainage, and effective antibiotics, with attention paid to both the aerobic and anaerobic components.

DR. MELLINKOFF:* Dr. Finegold, I thought there was a high incidence of gastric cancer in Japan, and I wonder whether the apparent rise in colonic cancer that you noted when the patients came here from Japan and changed to a Western diet is an effect of the diet that increases the incidence of colonic cancer or whether it simply reflects a reduction in gastric cancer. In other words, if somebody doesn't die of gastric cancer, does he then die of colonic cancer?

DR. FINEGOLD: Well, there certainly is a reduction in gastric cancer as well. Whether this is the only explanation or not I don't know, but I think this is probably not the major explanation. It is

*Sherman Mellinkoff, MD, Dean of the UCLA School of Medicine.

kind of discouraging, though, when you realize that the Japanese diet is very palatable and that it might be good for reducing the incidence of colon cancer, to think that it might increase the likelihood of gastric cancer, which is certainly a worse disease. Just what the mechanism might be in leading to stomach cancer is entirely unknown. It may be a function of the type of processing of food. The basic food itself may be fine for minimizing risk of colonic cancer, but perhaps something in the processing results in aflatoxins or other carcinogens that might account for the gastric cancer.

Question: Dr. Finegold, suppose a stool culture is submitted from a patient who has diarrhea and who hasn't been receiving antibiotics. The laboratory reports Staphylococcus aureus. What are the conditions that allow that to happen, aside from possibly some error in the procedure?

Dr. Finegold: Was this patient in hospital? Our experience is that it is uncommon to get S. aureus in the stool unless the patient has recently been receiving antimicrobial therapy, which suppresses some of his indigenous flora, allowing the staphylococcus to colonize. It is true that staphylococci and other potential pathogens—klebsiella and pseudomonas, for example—may colonize the upper respiratory tract in the absence of antimicrobial therapy in sick patients who are in hospital, and perhaps this happens in the gut too. Small numbers of staphylococci may be seen in the absence of disease, and the use of a highly selective culture medium might reveal them.

Question: Dr. Bartlett, your implications about flora in aspiration pneumonia are very interesting. Men in practice often treat these patients with penicillin. Since you isolated B. fragilis in ten cases, do you advocate another agent?

Dr. Bartlett: This is a difficult question—one that cannot be answered with currently available information. When we recovered B. fragilis it was always part of a complex flora which included other anaerobes as well. It is conceivable that antibiotic therapy directed against other components of the infection would be adequate. In our patients, having isolated B. fragilis, we were unwilling to test this hypothesis.

Question: Was there anything unique about the bacteriology of the various types of infections? Did any particular anaerobe show a propensity to cause a particular type of x-ray picture?

Dr. Bartlett: We have subsequently done that type of analysis by correlating the bacteriological results with the type of pathogenic process. To summarize the findings among 140 cases of anaerobic infection: There was no particular pattern for pneumonitis, empyema, or cavitating pulmonary infections. In other words, given the various forms of anaerobic infections, the bacteriology was similar both in total and specific isolates.

Dr. Clarke: Dr. Bartlett, I'd like to ask why there are so many anaerobes in the lung infections. Are you implying that there is overgrowth in the upper gastrointestinal tract in those patients; are those anaerobes in the food that those patients have eaten recently, or what?

Dr. Bartlett: Most of these cases of aspiration pneumonia presumably result from aspiration of oropharyngeal contents. The mouth harbors a very rich flora that includes both aerobes and anaerobes. In our laboratory, analysis of saliva in people with good dental hygiene yields five to ten anaerobes for every aerobe. The relative proportion of anaerobes would be even higher in the presence of dental infections. I assume that saliva is the inoculum in most patients with aspiration pneumonia.

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Refer to: Diabetic microangiopathy—Medical Staff Conference, University of California, San Francisco. West J Med 121:404-412, Nov 1974

Diabetic Microangiopathy

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It sometimes seems that the rarer a metabolic disease is, the more clearly we understand its pathogenesis. Unfortunately the obverse also seems to hold true. Despite the work of many investigators the pathogenesis of diabetes mellitus remains obscure. We shall hear today from Dr. Marvin D. Siperstein concerning diabetic microangiopathy, the most important concomitant of diabetes and a field in which he has made many personal contributions.*

DR. SIPERSTEIN:† As every clinician who is responsible for the management of the diabetic is very well aware, the major *clinical* problem in the management of diabetes mellitus is *not* the control of blood sugar. Perhaps no more than 20 percent of all diabetic patients ever require insulin for the adequate control of blood sugar. Moreover, probably fewer than 5 percent of all persons with diabetes die as the direct result of hyperglycemia and other carbohydrate abnormalities of diabetes. By contrast, both pathological and clinical reports have amply demonstrated that approximately 85 percent of persons with diabetes die of the vascular disease of diabetes mellitus. It is, then, the vascular disease, not the carbohydrate abnormalities, that we in the clinic have to cope with.

These vascular manifestations of diabetes are (1) a relatively specific form of renal disease, intercapillary glomerulosclerosis, first described in its nodular form by Kimmelstiel and Wilson;[1] (2) atherosclerosis, the most common cause of death among adults with diabetes; (3) diabetic retinopathy, with its microaneurysms, and retinitis proliferans, which probably represent the second or third most common cause of blindness in the United States today and (4) the leg ulcers, gangrene and accompanying neuropathy, which represent the most common problems that plague the adult with diabetes. This, then, is diabetes mellitus as clinicians see it today, and as I suspect clinicians saw it even in the preinsulin era, though clearly it was not so recognized. Diabetic retinopathy, it should be recalled, was widely recognized by clinicians only in the past 30 years.

It is now apparent to everyone who follows diabetic patients that these manifestations of diabetes progress rather inexorably, regardless of the degree of control. By the end of the third decade of hyperglycemia, the Joslin Clinic and all other centers have found that retinopathy develops in 70 to 80

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Marvin D. Siperstein, MD, PhD, Professor of Medicine; Director, Division of Pathophysiology, Department of Medicine; Senior Investigator, Cardiovascular Research Institute, University of California, San Francisco; Chief, Metabolism Section, Medical Service, Veterans Administration Hospital, San Francisco.

These studies were supported by USPHS grant AM-13866.

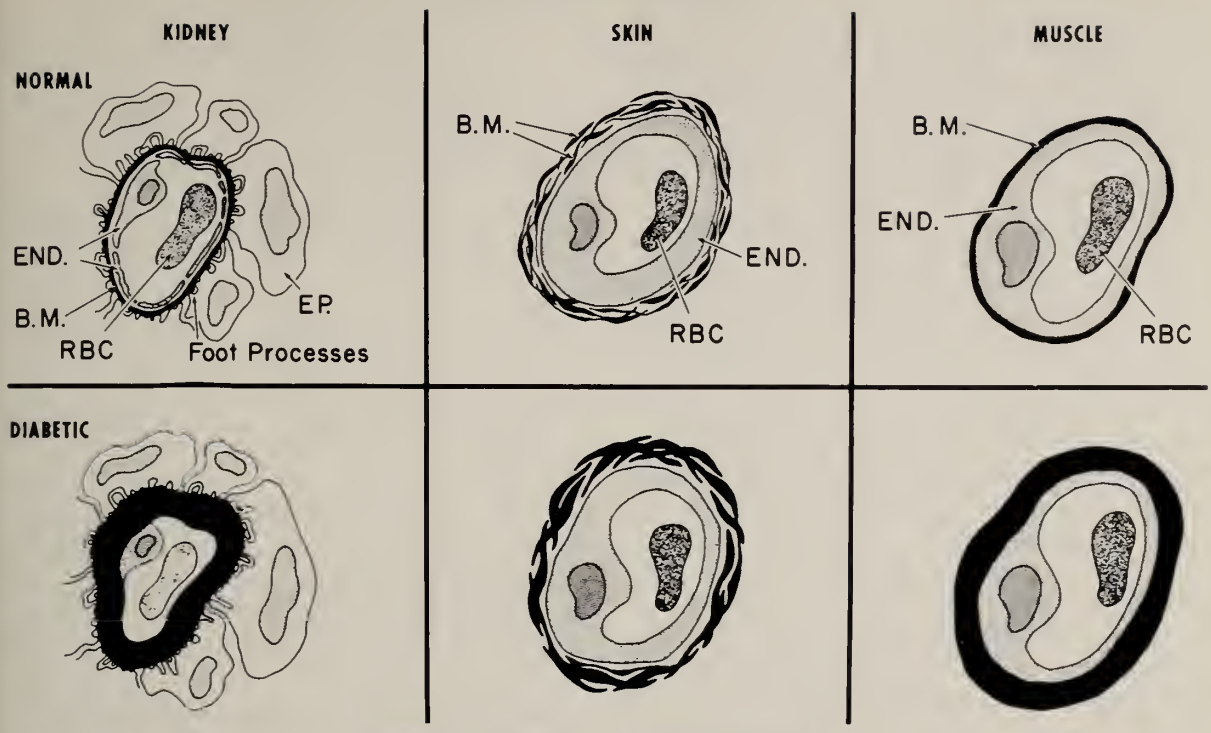


Figure 1.—Capillary basement membranes.

percent of persons with diabetes. I will not discuss today whether such an incidence curve can be shifted slightly to the left or a bit to the right by poorer or better control of the blood sugar. The fact remains that the best control does not prevent diabetic retinopathy. So the question that has been asked with particular intensity over the last two to three decades is, "what is responsible for the microangiopathy of diabetes?" What is its pathological basis and if possible what is its biochemical basis?

Clearly the major contributions to this field were first made with light microscopy by the ophthalmologist Friedenwald, who noted that the periodic acid-Schiff (PAS) positive nodule that Kimmelstiel and Wilson had described in 1936 really consists of a thickening of the capillary basement membrane. It was Friedenwald who first enunciated the unifying hypothesis that diabetic microangiopathy might be the equivalent of basement membrane thickening.[2] Bergstrand and Bucht[3] in 1957 and, independently, Farquhar, Hopper and Moon[4] at this institution two years later, reported that (as shown schematically in Figure 1) the earliest lesion in the diabetic kidney consists of a thickening of the basement membrane of the glomerular capillary. Such basement membrane hypertrophy progresses to engulf the epithelial and the endothelial cell and to encroach upon the lumen of the capillary. The pathological consequences of such basement membrane thickening in the kidney are obvious even by light microscopy. If this basement membrane thickening is focal, one sees the PAS-positive, nodular intercapillary glomerulosclerosis of Kimmelstiel and Wilson. If this process is diffuse throughout the kidney one sees under the light microscope the diffuse type of intercapillary glomerulosclerosis.

Measuring Basement Membrane Width

Everyone now agrees that the basic pathogenesis of diabetic renal disease involves thickening of the capillary basement membrane, be it peripheral or in the mesangial portion of the glomerulus. Many investigators, once these pioneering studies were published, asked the question, "can one quantitate diabetic microangiopathy by measuring the basement membrane width, and hence determine the degree of microangiopathy, in life?" Renal biopsy specimens are obviously difficult to obtain routinely, and the most accessible tissue, skin, has basement membranes that are laminated and difficult to quantitate. By contrast, as Zacks[5] was the first to show, muscle capillary basement membranes are relatively homogeneous, and (as shown again schematically in Figure 1) they demonstrate

thickening of the basement membrane just as does the kidney. The problem that became apparent to our group, consisting of Leonard Madison, Roger Unger and me, was how to obtain muscle during life and how to measure basement membrane widths reproducibly and objectively.

The first of these problems was solved relatively easily by adopting the Franklin-Silverman needle and taking a biopsy specimen from the quadriceps muscle halfway between the knee and the hip.[6-8] This is a fairly simple procedure, it takes five to six minutes, and it is probably less painful than a glucose tolerance test. The procedure has been generally adopted throughout the world, thereby eliminating the potential problem of interpreting variable results at different sites of biopsy. On the other hand there are unfortunately numerous methods of quantifying basement membrane width. The one that proved to be most objective and reproducible in our experience consists of overlaying 15 capillaries with 20 equidistant radiating lines, and at the point of contact of each of these lines with the basement membrane measuring this structure. The average of the 15 to 20 measurements is termed the quadriceps capillary basement membrane (QCBM) width.

Use of the QCBM Technique

While most of the several modifications of this technique that have been suggested yield adequate results, the only caution that must be observed is that the method of measurement should be objective. Obviously if one selects only the thinnest portion, or only the thickest portion of the basement membrane, one introduces a considerable error. I mention this because some investigators[9] measure only the thinnest portion of the basement membrane, and as we have recently documented,[10] this nonobjective procedure introduces a systematic error of approximately 30 to 40 percent. There is also an error in the objective random procedure of measuring all capillaries in that some capillaries will be obliquely sectioned. The resulting error, however, averages only a trivial 10 percent and for practical purposes can be ignored.

The results obtained by the QCBM method showed for the first time that persons with diabetes do in fact develop basement membrane thickening of their muscle capillaries—normal approximately 1,200 Angstrom units (Å), diabetic 2,400 Å.[7] This conclusion has subsequently been confirmed by everyone who has measured diabetic muscle capillaries.[11-15] The initial reports of Friederici and Schwartz[16] and Vracko,[17] indicating that there is no significant basement membrane thickening in diabetes, have both now been retracted.[13,18]

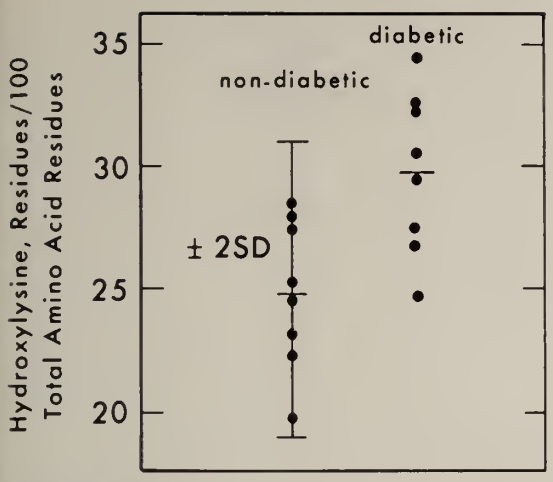
TABLE 1.—*Diagnostic Values for Muscle Capillary Basement Membranes*

←1,325 Å	1,600 Å→
Normal 96%	Normal 1%
Diabetic 1%	Diabetic 93%

TABLE 2.—*Prevalence of Muscle Capillary Basement Membrane Thickening in Adult Diabetes*

Author	*Year*	*Fixative*	*Number of Patients*	*Incidence Percent*
Siperstein ...	1968	Osmic	47/51	92
Vracko	1970	Osmic	9/9	100
Danowski-Fisher	1971	Osmic	9/9	100
Danowski-Fisher	1972	Osmic	6/6	100
Pardo	1972	Osmic	7/8	88
Siperstein ...	1973	Osmic	20/20	100
Williamson ..	1972	Glutaraldehyde	82/151	54
Yodaiken ...	1970	Glutaraldehyde	11/20	55
Siperstein ...	1973	Glutaraldehyde	9/20	45

Far more important from the standpoint of the clinician who wishes to use this method diagnostically, one must know the prevalence of this lesion in diabetic patients and how sensitive and accurate the procedure is (Table 1). The two critical figures in the QCBM technique are 1,325 and 1,600 Å (Table 1). Of normal subjects, 96 percent will fall below 1,325 Å, the false-negative error of the method is about 1 percent. By contrast, 93 percent of persons with diabetes have QCBM thickness greater than 1,600 Å and only 1 percent of normal biopsy specimens will yield false-positive results. The method then has proven to be extremely sensitive with an acceptable incidence of false-positive and negative values. All subsequent studies that have used this technique have confirmed these figures (Table 2). The two important points to emphasize in Table 2 are that these data are obtained in adults and second, that it is critical that the tissue be fixed in osmic acid.[10] As noted in Table 2, all investigators who fix their tissue in osmic acid find prevalence values for basement membrane thickening of from 88 to 100 percent. By contrast, if one fixes in glutaraldehyde, a very common and for most purposes an excellent electron microscopic fixative, one produces a relative



P<0.01 but

1) 5 of 8 diabetics are within normal limits
2) If omit one high point, P = NS

Chart 1.—Hydroxylysine in glomerular basement membrane (Beisswenger and Spiro, 1973[22]).

but variable swelling of the basement membranes and it becomes very difficult to measure. In part for this reason, the St. Louis group under Williamson finds only about half the prevalence of thickened basement membranes observed by our group. Yodaiken,[11] using glutaraldehyde fixation, also finds only a 55-percent prevalence of basement membrane hypertrophy, and in duplicate biopsy studies comparing both methods of fixation[10] we could confirm Williamson completely in that in glutaraldehyde-fixed tissues the sensitivity of the technique drops from the 92- to 100-percent prevalence observed in osmic acid fixation, to the point of detecting only roughly half of the persons with diabetes. So for this purpose it is critical, as everyone is finding, to fix tissues in osmic acid.

Biochemistry of Basement Membranes

The next question (which I wish to touch on only briefly, since we have so few answers in this field) is what is the underlying pathogenesis of basement membrane thickening and, hence, of diabetic microangiopathy? First, the thickening of the capillary basement membrane is clearly not accompanied by a thickening of the analogous structure that lines the muscle itself, in that the sarcolemma membrane lying only a few angstroms away from the capillary basement membrane escapes this lesion. One can frequently see collagenous fibers within the capillary basement membrane. Several biochemists, notably Lazarow,[19] Kefalides[20] and Spiro,[21] have analyzed basement membranes, and each has observed that basement membranes contain a high percentage of hydroxylysine and hydroxyproline. This structure, then, is made up of collagenous protein. One can in fact frequently see collagenous fibers within the capillary basement membrane. The major difference from structural collagen is that basement membranes contain a high fraction, approximately 10 percent, of carbohydrate. It had been hoped in our laboratory and by many other groups that some biochemical difference in amino acid structure between normal and diabetic basement membrane might be detected by suitable analysis. The only publication of such a finding is that of Beisswenger and Spiro,[22] who reported that diabetic basement membranes have a higher concentration of hydroxylysine than do normal basement membranes. As their data, shown in Chart 1, indicate, there is indeed a statistically significant difference in the mean hydroxylysine values of the eight diabetic and eight normal basement membranes. Unfortunately for the physiological implications of this observation, this difference depends entirely on the one high point in the diabetic group; moreover, only three of the eight diabetic subjects actually show significant differences in hydroxylysine. We have attempted to confirm this observation and have not succeeded;[23] moveover, three other groups have failed to find any difference in the amino acid composition of normal and diabetic basement membranes.[19,24,25] At this stage, therefore, we must conclude that there is simply no solid evidence to indicate a consistent biochemical change in the primary structure of the basement membrane of the diabetic kidney.

Limitations to the QCBM Method

From a theoretical standpoint it is also important to emphasize that basement membrane thickening in the patient with diabetes is not present at birth. As shown in Chart 2, recent studies in children have demonstrated that QCBM thickens with age in this younger group of diabetic patients,[26] less so in the age-matched control group, and then levels off in both groups at about age 20 (Chart 2). Below age 16 the prevalence of the lesion is not the 100 percent that one finds in adults. Depending on the age of the child, QCBM hypertrophy is seen in approximately 40 percent of young diabetic patients. It follows that a practical limitation of this technique is that in children a normal basement membrane width does

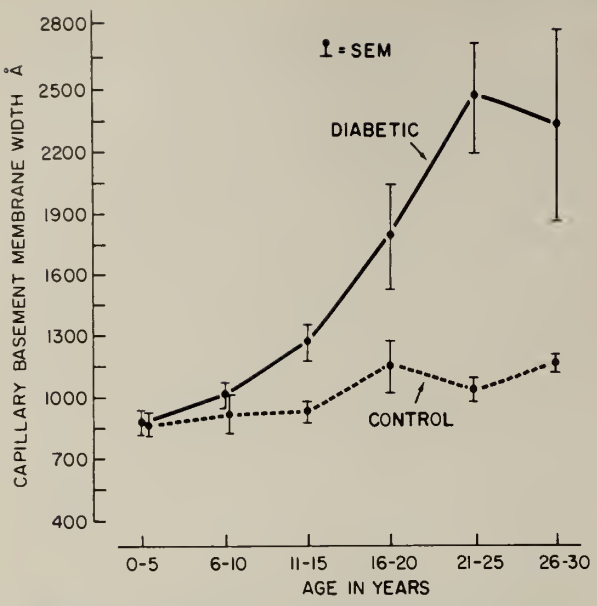


Chart 2.—QCBM width in diabetic and non-diabetic children.

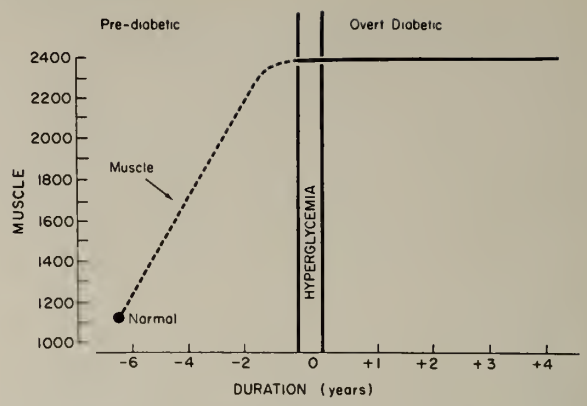


Chart 3.—Relation of muscle capillary basement membrane thickening to duration of diabetes.

TABLE 3.—*Absence of Relationship of Duration of Hyperglycemia to Capillary Basement Membrane Width*

Duration in Years	*Investigator*		
	Siperstein	*Williamson*	
	A	*A ± SD*	
0	2,497	1,268 ± 445	
1-4	2,297	1,100 ± 220	NS
5-9	2,455	1,265 ± 432	NS
10-19	2,430	1,519 ± 628	NS
20+	2,706	1,802 ± 374	P<.01

not rule out the presence of diabetes mellitus, which for practical purposes such a finding would do in an adult.

There is a second interesting limitation of the QCBM method. That is, as indicated in Chart 3, there is no significant relationship between duration of diabetic hyperglycemia and QCBM width. This is of course a disadvantage of the technique, in that certainly in the kidney and probably, as indicated earlier, in the retina there is an effect of duration of hyperglycemia upon the vascular manifestations of diabetes. On the other hand, this finding does indicate that diabetic microangiopathy can be dissociated from the hyperglycemia of diabetes. Incidentally, were there a correlation between duration of hyperglycemia and basement membrane width, this relationship would in no way constitute evidence that hyperglycemia *causes* basement membrane thickening, as some investigators have suggested. Obviously, such concomitance would simply suggest that there is a relationship, which might indicate that basement membrane thickening causes hyperglycemia or that these two lesions of diabetes are progressing in response to some common biochemical defect, or that they might be independent.

The second point to be made from Chart 3 is that at the time of detection of diabetes mellitus, the width of the basement membrane is already maximal. Moreover, the 93 percent prevalence figure is observed at the time of onset of hyperglycemia, just as it is ten years later. In other words, there is no progression of the prevalence of QCBM thickness with duration of hyperglycemia. By contrast, Williamson's group[12] has suggested that there is a progression of basement membrane thickening with duration of hyperglycemia, a finding which, if valid, would of course significantly improve the value of this method. Williamson's data (Table 3), accepting the error caused by the measurement of only the minimal points of the basement membrane, actually show, as do ours, that there is no significant thickening of quadriceps capillary basement membrane for at least 20 years of hyperglycemia. After 20 years there may be some increase in quadriceps capillary basement membrane width, but at this late interval this finding is of little help in predicting basement membrane thickening in the kidney or in the retina.

Interestingly, Williamson's data also confirm our finding that the majority of persons with diabetes already have significant QCBM thickening at the time of onset of hyperglycemia. The QCBM method is therefore very sensitive because the basement membrane in the muscle is already maximally thickened at the time of onset of overt diabetes, but there is a disadvantage in that one cannot use this technique as a practical method of predicting what is going on in other tissues. Im-

plicit in this observation, as indicated by the dotted line in Chart 3, is the conclusion that muscle capillary basement membrane thickening actually occurs before the appearance of clinical hyperglycemia.

Data From Induced Hyperglycemia

The dissociation of the carbohydrate abnormalities of diabetes and diabetic microangiopathy can be studied in a number of ways. Perhaps the most common approach is to attempt to determine whether induced hyperglycemia in animals will produce basement membrane thickening. Actually the only published claim of quantitatively significant thickening of capillary basement membranes in response to induced hyperglycemia is that of Bloodworth.[27] These data show that there is in fact no significant thickening of renal basement membranes of dogs maintained hyperglycemic for up to four years (3,111±413 vs. 3,760±326, $P>0.1$). The same can be shown in the retina (Table 4). Bloodworth and Engerman's data[28] indicate that there is an insignificant difference in the retinal basement membrane width of dogs kept alloxan-hyperglycemic for many years. We have carried out similar experiments in monkeys that were kept hyperglycemic for 12 years by Dr. G. E. Gibbs, yet developed no basement membrane thickening.[29] In summary, there are probably no experiments indicating that hyperglycemia per se in animals will produce objective thickening of the capillary basement membranes.

The same experiment is performed rather regularly in man, in that man, too, frequently "pancreatectomizes" himself—with alcohol—and as a result produces secondary hyperglycemia. As Table 5 indicates, despite many years of such severe hyperglycemia only one of 18 subjects with pancreatogenous hyperglycemia has developed microangiopathy as detected by a thickening of the QCBM to a width greater than 1,600 Å. This result contrasts strikingly with the 93- to 100-percent prevalence of basement membrane thickening that one sees in genetic diabetes mellitus.

The observation that secondary hyperglycemia does not produce basement membrane thickening has now been confirmed in at least two other laboratories. Camerini-Davalos and Bloodworth[30] have also noted that basement membrane thickening does not develop in patients with Cushing's disease. Danowski and Fisher[15] have observed that many causes of secondary hyperglycemia, including muscular dystrophy and myotonia dystrophica, do not lead to basement membrane thickening. Danowski has termed such nondiabetic hyperglycemia "pseudodiabetes." I would prefer simply to drop the name diabetes and call such conditions nondiabetic or secondary hyperglycemia.

The finding that secondary hyperglycemia does not produce basement membrane thickening suggests a second very practical use of the QCBM technique. Dr. Richard Havel and I have collaborated on a study examining patients with lipodystrophic "diabetes"[7] and find that their basement membranes are normal. While hyperlipemia develops in diabetic patients, it is important clinically to recognize that hyperlipemia is an important cause of secondary hyperglycemia. We have recently[31]

TABLE 4.—*Retinal Capillary Basement Membrane Widths in Alloxan-Hyperglycemic Dogs*

(Age 6 years and over)
Bloodworth and Engerman, 1971

Hyperglycemia Å		*Control* Å	
3,000	3,150	3,400	3,250
1,875	2,200	3,000	1,900
2,300	2,900	2,800	2,700
2,475	3,400	2,750	2,500
5,100	3,500	2,300	1,800
2,450	4,100	2,195	
2,700	5,500		
Average 3,189 ± SE 286		2,600 ± SE 156	

"Diabetic" vs. Control = not significant

TABLE 5.—*Basement Membrane Width in Pancreatic "Diabetes"*

Age/Sex	*Diagnosis*	*FPS mg per 100 ml*	*Basement Membrane Width Å*
1. 24♂	Chronic Pancreatitis	531	1,219
2. 31♂	Chronic Pancreatitis	400	1,028
3. 41♂	Acute Pancreatitis	453	1,039
4. 45♂	Chronic Pancreatitis	200-300*	796
5. 45♂	Chronic Pancreatitis	298	2,344
6. 46♂	Chronic Pancreatitis	364	1,000
7. 49♂	Chronic Pancreatitis	320	1,428
8. 49♂	Chronic Pancreatitis	236/2 hr	1,167
9. 36♂	Chronic Pancreatitis	242	1,250
10. 50♂	Chronic Pancreatitis	236	1,066
11. 58♂	Chronic Pancreatitis	168	1,069
12. 38♂	Pancreatitis	250	865
13. 36♂	Acute and Chronic Pancreatitis	350	1,465
14. 46♂	Chronic Pancreatitis	490†	960
15. 48♂	Chronic Pancreatitis	290	951
16. 65♂	Chronic Pancreatitis	368	1,050
17. 30♂	Chronic Pancreatitis	340	1,040
18. 32♀	Chronic Pancreatitis	350	998
			Avg. 1,152

*Fasting hyperglycemia for 13 years.
†Fasting hyperglycemia for 6 years.

TABLE 6.—*Progression of Basement Membrane Thickening in a Prediabetic Patient*

Date	Glucose Tolerance F	1 hr	2 hr	Basement Membrane Width Å
1964	100	130	78	975 ± 102
1968	93	119	104	1,367 ± 88
1972	78	132	72	2,104 ± 222

shown that the QCBM method can be very useful in determining which patients do in fact have diabetes and which simply have hyperglycemia secondary to hyperlipemia.

What I have said up to this point is that neither in animals nor in man does hyperglycemia produce basement membrane thickening, a lesion which is for practical purposes a *sine qua non* of genetic diabetes mellitus. If, as we are implying, the carbohydrate abnormalities of diabetes really can be dissociated from the microangiopathy of diabetes, another way of looking at this relationship is to examine a group of geneticaliy diabetic subjects in whom the carbohydrate abnormalities of diabetes have not yet developed. If diabetes is inherited as an autosomal recessive trait, it should ultimately develop in the offspring of two diabetic parents in all cases. If diabetes is inherited in a multifactorial manner, then according to Neel[32] approximately 75 percent of the offspring of two diabetic parents should ultimately become overtly diabetic. Whatever the mode of inheritance, the prevalence of diabetes in a group of offspring of two diabetic parents is high. We therefore selected some 30 prediabetic subjects, screened them carefully by repeated glucose tolerance tests and eliminated those who showed any abnormalities. Consequently, in these persons there are perfectly normal results from glucose tolerance tests, normal insulinogenic indices and normal growth hormone levels. But they did not have normal basement membranes.

Variance analysis is used in this study since the lesion does not start uniformly in every capillary nor uniformly around the circumference of each capillary; and variance analysis simply picks out such focal and segmental lesions. By this technique, 74 percent of the prediabetic subjects showed significant basement membrane thickening.[8] This finding led to the suggestion in 1968[7] that at least in adults the microangiopathy of diabetes may well precede the hyperglycemia of diabetes. A critical question that had to be asked is, "What happened to the 26 percent of prediabetic patients who did not have basement membrane thickening in the original study?" If followed over the years would microangiopathy also develop in these persons before the onset of carbohydrate abnormalities? We have then followed at least 21 of these patients over the past eight years. Data for one such patient are shown in Table 6.

Glucose tolerance measured in 1964 was perfectly normal and basement membrane width was also normal. By 1968 the basement membrane had begun to thicken despite the fact that the glucose tolerance remained normal. However, in 1972, the patient's basement membranes had thickened into the diabetic range (well above 1,600 Å). Results of a glucose tolerance test in 1972, if anything, were better than in 1964, but the basement membrane thickening was now unequivocal. A summary of the results in all such prediabetic patients indicates that both basement membrane width and prevalence of significant QCBM thickening increased over this eight year follow-up period; in fact, the prevalence of this lesion is now at 90 percent. We are therefore approaching in the prediabetic population the figure for QCBM hypertrophy that we see in the overtly diabetic patient. Incidentally, some five of these patients have now become diabetic as judged either by severe abnormalities in glucose tolerance or by development of overt diabetes mellitus.

This study then indicates that, first, if one does prospective studies on such prediabetic patients, basement membrane thickening does progress from that seen initially in prospective studies on such prediabetic patients and, second, ultimately some 90 percent of such prediabetic subjects will develop microangiopathy as detected by this technique. The question then arises as to whether microangiopathy is *clinically* detectable in prediabetic patients. We have recently screened all patients coming to a large ophthalmology clinic for any evidence of retinal microangiopathy.[33] Thirteen patients with such lesions but with normal glucose tolerance tests were examined by the quadriceps muscle capillary basement membrane method and eight were found to have significant basement membrane thickening. So by this independent measure we would suggest that clinically significant microangiopathy, too, may precede overt hyperglycemia in many more persons with diabetes than had previously been suspected. These patients will obviously have to be followed over the years to see whether in fact they develop overt diabetes mellitus, but this type

of data indicates that basement membrane thickening and microangiopathy of clinical significance may precede the hyperglycemia or detectable carbohydrate manifestations of diabetes mellitus.

Summary

The quantitative method of measurement of quadriceps capillary basement membrane width does provide a sensitive and reasonably specific means of objectifying diabetic microangiopathy, and gives one an independent marker for genetic diabetes mellitus. A second and important practical use of the technique is to differentiate secondary hyperglycemia from genetic diabetes mellitus. With the obvious genetic and pathologic differences in these two causes of hyperglycemia, this distinction becomes of increasing clinical significance.

Two limitations of the method must be emphasized. First, basement membrane thickening should not be used to diagnose prediabetes in individual patients. I think it is too early, despite the 90- or 74-percent figures, to use the technique in this way. Second, as we have repeatedly emphasized, the method does not predict the degree of microangiopathy in other tissues. I wish that Williamson's conclusion that the QCBM width is correlated with duration of hyperglycemia were correct, but I do not think it is. Third, one cannot use this procedure to rule out diabetes in young children. If the result is negative in a child, it does not mean, as it does in adults, that genetic diabetes mellitus is absent. If, on the other hand, the biopsy is positive, the lesion would have the same implications as it would in an adult.

From a theoretical standpoint, these observations strongly indicate that diabetic microangiopathy is independent of the carbohydrate abnormalities of diabetes mellitus. Whether basement membrane thickening may cause hyperglycemia is a far more complicated question. Obviously, if one implies that basement membrane thickening is truly primary, one must ask the question, "How can a thickening of the basement membrane cause hyperglycemia?" It is not surprising, as we have previously shown,[34] that capillaries supplying the islets of the pancreas also show this lesion. It is conceivable, therefore, that the microangiopathy that afflicts every other tissue of the body may by involving the islets of the pancreas influence the relationship of blood glucose to insulin secretion. The latter point is obviously still clearly speculative. At this time all that can be stated is that our data as well as those of Kilo and Williamson support the conclusion that hyperglycemia can be dissociated from, and so does not appear to be causally related to, the microangiopathy of diabetes.

The implications of these findings for the future I view rather optimistically. Clearly, if we know what causes basement membrane thickening we are going to be much closer to answering the question of what causes diabetic microangiopathy, be that microangiopathy independent of the carbohydrate abnormalities as I am suggesting, or even if caused by the carbohydrate abnormalities as is obviously still widely believed. But it is clear that only through an understanding of why basement membranes thicken in persons with diabetes will we one day be able to say what causes diabetic microangiopathy and, it is hoped, even what causes diabetes mellitus.

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American Medical Association to Sponsor 16th Conference on the Medical Aspects of Sports

THE 16TH CONFERENCE ON THE MEDICAL ASPECTS OF SPORTS, sponsored by the American Medical Association under the auspices of its Committee on the Medical Aspects of Sports, will be held in Portland, Oregon, at the Memorial Coliseum on Saturday, November 30, 1974. The Conference is held annually in conjunction with and on the first day of the Clinical Convention of the American Medical Association.

Major highlights of the 16th Conference will focus on: International sports medicine, Jesse Owens, and female athletics.

Additional topics to be discussed are: The effect of local steroid injections on tendon strength, hockey injuries, allied medical care, skiing safety progress, emergency first aid and comprehensive community programs.

The Conference is open to key athletic personnel, allied medical specialists, and interested physicians. For further information write:

THE COMMITTEE ON THE MEDICAL ASPECTS OF SPORTS
535 N. Dearborn St., Chicago, Illinois 60610

Important Advances in Clinical Medicine

Epitomes of Progress— Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Preventive Medicine and Public Health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Preventive Medicine and Public Health which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Resurgence of Lice and Scabies

EVEN THOUGH ectoparasitic infestations are not reportable diseases, public health departments in the past few years have been made aware that both scabies and lice are again appearing in epidemic proportions in the population. Statistics are inaccurate, but those outbreaks that are reported via schools and public health clinics indicate a need for control measures.

Control measures for ectoparasitic infestations, scabies and lice, consist of education, treatment and prevention. Therefore, when a primary case of either disease is diagnosed, not only should the patient be treated but a short explanation of how scabies and lice are transmitted and spread should follow.

At present, the preferred and most common method of treatment is use of some form of the pesticide gamma benzene hexachloride. For use on humans, this is a prescription item and can be purchased as Kwell® cream, shampoo or lotion. Lindane, its over-the-counter disinfectant form (formerly available as a powder or lotion), can be purchased as an aerosol spray, Linofly®. Use of this form in treatment is effective since it kills both the adult parasites and their ova (nits of lice). In treating the patient, one must use effective therapy against the parasites both on the human as well as on their fomites.

Several useful medications for treating ectoparasites can be purchased over-the-counter.

- Sulphur ointment, B.P. (10 percent sulfur) —can also be used in a vanishing cream base. Marketed sulfur soaps have little effect.
- Dimethyl-diphenylene disulphide (dimethyl-

thianthrene) formerly marketed as Mitigal.® Very effective treatment. Expensive. Can be used in concentrations from 10 to 100 percent without causing dermatitis.

• Benzyl benzoate emulsions—At least a 20 percent concentration is necessary for 99 percent effectiveness.

In the treatment of scabies and lice, one must always take into account that by the time the patient is first diagnosed and treated with a proper medication for the parasites, they may well have a secondary pyoderma or eczematoid dermatitis. The therapeutic regimen for the patient, therefore, should take into account all of these factors.

STEPHAN BILLSTEIN, MD, MPH

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The Prevention of Erythroblastosis Fetalis

ERYTHROBLASTOSIS FETALIS due to Rh incompatibility is now a fully preventable disease. A recently published report of the World Health Organization (WHO) Scientific Group, *Prevention of Rh Sensitization,* summarizes both the rationale and the techniques that must be applied. Other authors have also pointed out how these recommendations should be incorporated into the practice of clinical preventive medicine by all those caring for pregnant women.

THE WHO RECOMMENDATIONS

• All Rh-negative women who are not already immunized to Rh and who give birth to an Rh-positive infant should receive a dose of anti-Rh. This dose should be judged according to the titer of anti-Rh in a woman's serum. The inhibitory effect of this anti-Rh is only transient so that a dose given at the time of a first delivery will have no effect on immunization following a later pregnancy. Therefore, the dose must be given after each pregnancy.

• D^u women should not be treated with anti-Rh since most of it will be absorbed onto the D^u cells, leaving very little to react with the infant's red cells. In addition, the risk of formation of anti-Rh in a D^u woman is extremely small.

• Rh-negative women who have abortions should receive a dose of anti-Rh, unless it is shown that the conceptus is Rh-negative.

• Anti-Rh should be given to all non-immunized Rh-negative women following any incidents during pregnancy where appreciable transplacental bleeding (for example, external version, amniocentesis and antepartum hemorrhage) can be anticipated.

• The presence in the recipient of other blood group antibodies, such as anti-K, is not a contraindication to giving a dose of anti-Rh.

• The presence of immunoglobulin preparations of other red cell antibodies, such as anti-C, anti-E or anti-K, is unimportant and it is unnecessary to cross-match the immunoglobulin against the recipient's red cells. On the other hand, cross-matching may be used as a method of detecting a large transplacental hemorrhage.

• Anti-Rh immunoglobulin should be given as soon as possible after delivery and within 72 hours whenever possible. It can be given either intramuscularly or, if suitably prepared, intravenously. When the intramuscular route is used, care should be taken to avoid injection into adipose tissue.

JOSEPH STOKES III, MD

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Influenza Vaccines 1974

AT PRESENT only inactivated influenza vaccines are licensed for use in the United States. In recent years, these vaccines have been more standardized and have contained fewer impurities. Some of these vaccines are produced using recombination techniques which cut production time from six months to less than four weeks and increased the yield of virus particles by a factor of ten. These vaccines stimulate production of serum antibodies and nasal neutralizing antibodies against the viral strains they contain. Their effectiveness is estimated at 70 to 80 percent.

Most influenza vaccines are manufactured during the first half of the calendar year in preparation for distribution in the fall months. These vaccines are bivalent, containing inactivated virus particles from antecedent and prevalent strains of

Influenza A and B. For the coming 1974-75 season, only one dose of the bivalent influenza vaccine will be recommended for adequate protection. Two injections (one of each of two vaccines) were necessary during the 1973-74 season as the disease potential of the Hong Kong strain of Influenza B was not realized until the spring of 1973 and it was too late to incorporate it into the already manufactured bivalent vaccine produced for the 1973-74 season.

Live vaccines are still in the developmental state and demonstrate varying degrees of protection. Side effects vary from no clinical systemic signs to minimal upper respiratory symptoms.

The following table is a brief summary of the current status of live influenza vaccines.

STEPHAN BILLSTEIN, MD, MPH

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Scombroid Poisoning from Mahi-Mahi

RECENT OUTBREAKS have shown that spoiled mahi-mahi prepared from dolphin fish (family Coryphaenidae) can cause acute food poisoning with characteristic symptoms previously believed to be associated only with the Scombroidea family of fishes (for example, tuna, mackerel, bonito, albacore, skipjack). Symptoms include nausea, vomiting, diarrhea, abdominal cramps, swelling and flushing of the face, oral burning and blistering, thirst, metallic or peppery taste, pruritis, severe throbbing headache and urticaria. Thus, the patient appears to have both an allergic reaction and a gastro-intestinal upset. The disease is typical of chemical poisoning in that the incubation period is brief, ranging from a few minutes to one hour. The cause is related to spoilage, whereby bacteria break down the histidine in the flesh of those species that can cause disease. The spoilage may be so minimal that it is not obvious to the patient.

The disease is usually self-limited with relief in 8 to 12 hours. Treatment with antihistamines or sympathomimetics (for example, epinephrine

Current Status of Live Influenza Vaccines

Research Group	*Vaccine Type (Production method)*	*Clinical Effect on Recipients*	*Degree of Protection Against Wild Virus Infection*
1. Chanock RM, et al National Inst. of Allergy & Infectious Disease	Temperature sensitive variant. Grows at lower temperature than wild virus. Produced by use of 5-fluorouracil acting on previous wild virus strain (1965A_2, HKA_3).	25 percent volunteers have mild upper respiratory infection symptoms.	100 percent in those volunteers challenged with wild virus.
2. Davenport FM, Massab HF University of Michigan	Temperature sensitive variant. Older, mouse-adapted influenza subtype was used.	?	?
3. Kilbourne ED Mt. Sinai Hospital, New York, N.Y.	Vaccine against neuraminidase antigen. Used recombination techniques. "Infection-permissive" immunization.	Mild symptoms in some recipients.	Trials under way.
4. Hannoun C Pasteur Institute, Paris	Point variant that no longer mutates. Grow current circulating strain in presence of antibodies specific for variant.	Minimal.	Percentages not available.
5. Russian vaccines	A. Intranasal allantoic fluid attenuated virus.	Reactogenic. Limited to adults 16 and older.	Poor.
	B. Oral tissue culture fluid (chick embryo kidney cells).	Given as drink to 1 year and older	Poor.
6. Smith, Kline and French	Live attenuated form of A_2 (Eng 42/74). Administer intranasally with drops or nasal spray.	No symptoms Non-spreading Antigenic yields good nasal and serum ABY response.	Trials under way with wild influenza virus challenge (including Eng 42/74 and Australia 73).

hydrochloride), along with supportive care, has been found to be helpful. The syndrome can easily be confused with "Chinese restaurant syndrome."

The local health department should be notified promptly when scombroid poisoning is suspected, as preventive action can frequently be taken by removing any suspect fish from the marketplace.

DONALD G. RAMRAS, MD

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New Guidelines for Determining When Tuberculosis Patients Are No Longer a Public Health Risk

THE CALIFORNIA CONFERENCE OF LOCAL HEALTH OFFICERS, on the recommendation of the California Tuberculosis Controllers Association, recently adopted new guidelines for determining when tuberculosis patients are no longer a public health risk in the community and thus can be released from all restrictions on their activities.

GUIDELINES

Tuberculosis patients under certain conditions, even though still harboring viable tubercle bacilli, present a minimal hazard of disease transmission to others in the community. It is believed that in cases where the criteria listed here are fulfilled, the patients present such an insignificant risk to the community that restriction of their activities is not justifiable.

Criteria

- The patient has had at least one month of continuous, adequate chemotherapy with at least two drugs to which his organisms are sensitive.
- The patient has responded to treatment both clinically and radiologically and is asymptomatic.
- The patient is now, and can be expected to remain, under medical supervision for his disease.
- The patient is cooperative and understands the nature of his disease, and it can be expected that he will continue on drug therapy and that the prescribed drugs will be available to him for the necessary period of time.
- The patient's home situation has been evaluated by public health personnel and is considered suitable for such a patient.
- The patient's sputum has been examined by concentration and culture by approved public health laboratory methods, and at least three consecutive concentrated smears have been negative.

It is emphasized that these are *guidelines* only. In all instances the local health officer has discretion and final responsibility for the control of communicable diseases within his jurisdiction.

DONALD G. RAMRAS, MD

REFERENCE

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Amniocentesis

TRANSABDOMINAL AMNIOCENTESIS, a technique used in the latter stages of pregnancy to prevent Rh hemolytic disease and respiratory distress syndrome, can also be used earlier (about the 15th week of gestation) to detect certain genetic disorders and allow their prevention by therapeutic abortion. Experienced genetic screening centers have found amniocentesis to be a remarkably low-risk procedure. The recent introduction of ultrasonic placental localization has reduced fetal hazards even further.*

There are several situations in which amniocentesis should be considered.

- *Chromosomal Disorders.* The risk of Down's syndrome, as well as other chromosomal disorders, increases with maternal age and with a history of previous affected offspring. The risk of bearing a child with Down's syndrome is about 1 in 2,000 for women in their 20's, 1 in 300 for women in their 30's and 1 in 40 for women in their 40's. Therefore, amniocentesis has been advised for women over age 35, or those who have had previous chromosomal anomalies such as Down's syndrome. It is advised particularly when parents are known carriers of chromosmal translocations.
- *Metabolic Disorders.* A number of inherited metalobic disorders, such as Lesch-Nyhan syndrome, galactosemia, lysosomal acid phosphatase deficiency, mucopolysaccharidosis, Pompe's disease, Tay-Sachs disease, Niemann-Pick disease, Fabry's disease and methylmalonic aciduria, have been specifically identified by amniocentesis. Be-

*HEW's Division of Biological Effects, Bureau of Radiological Health has just initiated a survey of women exposed during 1972 to determine whether ultrasound has any adverse effects on the mother or fetus.

cause of the recessive nature of these enzyme disorders, they appear unexpectedly in the offspring of normal parents, who are alerted, unfortunately, only after they have produced at least one affected child. Future efforts to eliminate such risks entirely will depend upon the success of heterozygote screening methodology. Although such screening would involve a much larger population sample, cost benefit analyses—comparing diagnostic expense with treatment and institutional expenses—usually show a favorable economic ratio.

• *X-linked Disorders.* No specific methods exist for the detection of serious disorders such as hemophilia or Duchenne's muscular dystrophy. However, a carrier mother who wishes to avoid the risk of producing an affected male offspring can have the sex of the developing fetus determined by amniocentesis and undergo selective abortion to give birth only to female children. This application of amniocentesis will tend to increase as reproductive compensation leads to a rising proportion of female heterozygotes in subsequent generations.

• *Congenital Malformations.* Recently, alpha-fetoprotein elevations have been noted in amniotic fluids associated with anencephaly and meningomyelocele. Since the recurrence risks of such malformations in a family is greater than that of the general population, amniocentesis may prove to be of value in preventing additional cases.

LAWRENCE J. SCHNEIDERMAN, MD

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Urinary Tract Infections In Children

THE SIGNIFICANCE, diagnosis and management of urinary tract infections (UTI) in children continue to be subjects of major controversy.

Whereas the long-term sequelae of urinary tract infections and especially their relationship to chronic renal failure, prematurity, neonatal mortality and hypertension remain unclear and need further study, the importance of the subject at this time is two-fold: (1) the recognized propensity of UTI to cause chronic ill health in children and (2) the known association of UTI with urinary tract anomalies in children, for which they therefore act as a useful indicator.

The prevalence of UTI is now known to be considerable: 12 to 20 out of any 1,000 school age girls have UTI at any one time. The incidence in boys (except in the first year of life and in the prostatic age group) is insignificant.

UTI diagnosis is hampered and delayed for several reasons. (1) Symptoms are often absent or non-specific. A high index of suspicion is therefore essential and the disease should be actively searched for in known target populations, for example, sick children, children with known congenital and acquired defects associated with UTI and those who have a past history of UTI. (2) Traditional laboratory methods of diagnosis are inaccurate (routine urinalysis) or expensive (urine cultures and sensitivity). Significant bacteriuria is now recognized to be the only reliable diagnostic criterion. Readily available screening methods which are simple to use, inexpensive and of proven reliability make the application of this criterion practical. (3) Collecting accurate urine specimens from children is difficult. Reliance on multiple rather than single specimens, close attention to details of perineal cleansing and judicious use of suprapubic aspiration are methods helpful in overcoming this problem.

The policy of radiologic investigation with excretory urograms and voiding cystourethrograms of all children (after even their first UTI) is becoming more generally accepted. Vesico-ureteral reflux is the most common anomaly uncovered, and it is the one problem associated with urinary tract infection that is known on occasion to lead to progressive renal disease (atrophic pyelonephritis also referred to as reflux nephropathy). However, there is agreement that not all patients with vesico-ureteral reflux require major operation or even invasive urologic instrumentation, as minor degrees of this anomaly are often reversible and certainly pose little danger of progressive renal damage. The policy of conservative expectant follow-up is recommended. Procedures such as ureteral dilation, internal urethrotomy, meatotomy and bladder neck reconstructive procedures, are being over-used without clearcut indications or definite evidence of their efficacy.

The recurrent nature of UTI has been emphasized and the need for careful persistent long-term follow-up with serum urine cultures is generally recommended.

Until the long-term sequelae, methods of diag-

nosis and follow-up, indications for operation and "state of the art" for managing this condition are more generally known and applied, there are serious questions as to whether mass screening for UTI should be employed.

RALPH D. HARRIS, MD

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Immediate Post-Partum Immunization for Rubella

THE NATIONWIDE EFFORT begun in 1969 to control rubella and prevent its teratogenic effects was focused on the immunization of children from a year to 12 years old. It was expected that the "herd immunity" thus established would protect non-immune women of child bearing age. Several recent epidemics among adolescent and college-age students have raised doubts about the validity of this concept. Recently, the United States Public Health Service has reported the desirability of extending the use of rubella vaccine to adolescent girls and adult women who have been shown serologically to be non-immune to rubella. In this group it is necessary to prove non-pregnant status and to assure prevention of pregnancy for at least two months and preferably three.

The ideal time for immunizing non-immune women is in the immediate postpartum period when non-pregnant status is certain and is likely to continue beyond the time that infection with the vaccine virus is a hazard. It would also be advisable to prescribe an effective method of contraception for at least three months following vaccination.

GENEVIEVE L. JOY, MD

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Coronary Heart Disease Prevention

The Multiple Risk Factor Intervention Trial (MRFIT)

CORONARY HEART DISEASE remains the leading community health problem in the nation. To control this epidemic we must direct our attention to primary prevention. American men are at higher risk than women, having one chance in five of developing the disease before the age of 60. Other than age and sex, the most important risk factors, convincingly established by a multitude of prospective studies, are elevated serum cholesterol, elevated blood pressure and cigarette smoking. Results of recent studies in behavioral sciences, nutrition and clinical trials indicate that these three risk factors can be modified. The expectation is great, therefore, that alteration of these risk factors can reduce the incidence rate of coronary heart disease. This is the main objective of MRFIT.

The Multiple Risk Factor Intervention Trial is being conducted, under National Heart and Lung Institute auspices, in twenty clinical centers in the United States, and will continue for a perod of six years. Its main objective is to determine whether a safe and systematic intervention aimed at altering the risk factors among men aged 35 to 57, who are at risk, will result in a significant reduction in the incidence of coronary heart disease death.

Selection of volunteers who wish to participate in the program is by three screening procedures and randomization of participants into special intervention (cases) and regular (control) groups. Both groups will be followed for six years. There are three centers in California, one at the Pacific Medical Center in San Francisco, one at the University of Southern California in Los Angeles and the third at the University of California School of Medicine at Davis in the Sacramento area.

It is hoped that practicing physicians will lend their support to this important community health program. If this program demonstrates a reduced mortality among those in the special intervention group, it will constitute a major advance in our capabilities to achieve primary prevention of coronary heart disease, and perhaps help bring this tragic epidemic under control.

NEMAT O. BORHANI, MD

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Contributions of Free Clinics to Public Health

FREE CLINICS (which began in 1967), were started largely because the health care system was not providing adequate medical care to certain population groups: primarily young people, minority groups, poor people and students. The term free clinic does not refer solely to facilities which provide free care. A free medical or dental clinic is generally independent of the regular health agencies, often operates with some volunteer staff and offers services without red tape or eligibility tests. Most free clinics encourage consumer participation and many were started directly by consumers who did not have access to health care.

The main types of free clinics can be classified as *neighborhood* (many started by blacks, Chicanos, Asians, Indians or poor whites), *street* (originally concentrating on drug-related illnesses), *youth,* (primarily offering venereal disease and hepatitis care and counseling), and *women's* clinics (providing health education, preventive care, family planning help and treatment for gynecological problems).

Free clinics have blazed a trail in several areas: notably care for venereal disease, hepatitis, drug abuse, family planning, health education and problem counseling. The Los Angeles County Health Department's youth clinics were modeled after local free clinics when it became apparent that young people were flocking to free clinics while largely ignoring the established health department clinics which were offering similar services.

The major contribution of free clinics is the demonstration that community people can take the initiative in meeting some of their health care needs through organizing their own facilities. Clinics started by ethnic minorities have provided acute, prenatal and well-child care to entire families in a dignified and compassionate manner. The massive epidemic of venereal disease and drug-related illnesses of the past few years indicates that established public health agencies and private physicians could not cope with these problems alone. Free clinics took major responsibility for these illnesses and, being "free," could assume the lead in meeting other health care needs, such as dispensing family planning materials, detecting lead poisoning, testing for sickle cell anemia and providing care to disadvantaged people in their own neighborhoods.

In health education, free clinics have developed new ways of counseling and educating the public about drug abuse. Some free clinics have comprehensive drug clinic care, rarely available elsewhere in the community. Another free clinic contribution is the training and use of para-professionals to successfully provide health services. The activism of medical students, nursing students and recent medical graduates; the changing attitudes of public health agencies and medical schools and the availability of revenue sharing has brought free clinics into cooperative relationships with health departments, hospitals and medical schools. Free clinics have earned a place in the health care system. Their survival will depend on the willingness of other health care institutions to accept them and to make a place for them in the development of any national health program.

JEROME L. SCHWARTZ, DPH

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Environmental Asbestosis as a Risk Factor

INHALATION OF ASBESTOS produces five important reactions.

1. Asbestos (or ferruginous) bodies in sputum or tissues represent secretion of material on asbestos *fibers* to, presumably, reduce their irritancy.

2. This is of no known clinical importance. With long continued exposure, asbestosis of the lung—a form of pneumoconiosis—is produced, with clinical manifestations similar to other pulmonary fibroses.

3. Among cigarette-smoking workers with 20 or more years of exposure, an exceptionally high rate of bronchogenic-cancer develops. This rate is roughly ten times that of age- and sex-matched groups of smokers.

4. Among such groups there is a several-fold excess of gastro-intestinal cancer.

5. Malignant mesothelioma of pleura and of peritoneum in about three-fourths of the cases is associated with asbestos exposure.

Cigarette smoking doesn't appear to play a role.

A substantial portion of the recorded cases is made up of wives of asbestos workers or residents living near industries that use asbestos. This suggests that a very fine particle with a long path may be involved. This could be the ultra-microscopic fibril that is detectable by electron microscopy.

With a clear record of potential harm, asbestos must be used more carefully than in the past. It is widely used in roofing, insulation, pipes and filters. It also is used in motor vehicle brake lining. It is naturally present in drinking water from reservoirs and wells in serpentine rock formations. Water transported in asbestos cement pipe may pick up asbestos. Some types of talc contain asbestos. Careful evaluation of new developments and processes involving asbestos or serpentine is indicated to avoid unnecessary exposure to this material.

JOHN R. GOLDSMITH, MD

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Berkeley

EDITORIAL

A Consensus at Last

After reading the three papers on urinary tract infections prepared by the Stanford University group, which appear in this issue of The Western Journal of Medicine, I believe that at long last a consensus has been reached in this complex and often controversial field. It is not entirely coincidental that three books on urinary tract infections were published during the past few years.[1-3] Each has its own unique approach to the problem and special contribution to be made, but the overall principles are remarkably similar. My own special delight is that pediatricians and internists with specialty interests in infectious disease, radiologists, pathologists and urologic surgeons all over the world are beginning to speak a common language about urinary tract infections. One of the major factors responsible for this synthesis has been a series of international symposia on pyelonephritis,[4-8] beginning with that convened by Kass and Quinn at Henry Ford Hospital in Detroit in 1959.

It would serve no useful purpose here to review all the important points brought out by the Stanford workers. You can read the abstracts as well as I. Rather, I would like to address myself to two problems that require further mutual understanding. These deal with (1) the natural history of nonobstructive urinary infection in females and (2) standardization of the urologic approach to these infections.

There is now general agreement that, for the most part, female patients with recurrent urinary tract infections generally do not end up with end-stage renal disease. Furthermore, urinary tract infections rarely lead to hypertension unless they cause major renal damage. This view is supported by a number of autopsy studies[9,10] and by several reports describing long-term observations of well documented cases.[11-13] Furthermore, when one examines data on patients undergoing chronic dialysis or renal transplantation, pyelonephritis accounts for 12.7 and 14.1 percent respectively of the major causes of renal failure.[14,15] In most of these patients, however, end stage disease develops because of severe obstructive, congenital or neurologic lesions.

Some investigators have interpreted these observations to mean that urinary tract infection in females is not a significant problem and deserves little attention. In my opinion this is a short-sighted view, for the following reasons: (1) Urinary tract infections in females account for tremendous morbidity. Episodes are often recurrent and frequently cause extreme discomfort. (2) Among the large group of females with symptomatic or asymptomatic infection are a small proportion, at least 5 percent in school girls, who do have important correctable structural or neurologic problems. These include severe grades of reflux in girls, various neurologic lesions affecting bladder function and infection stones. The important point is that these persons usually cannot be distinguished from patients who do not have lesions, without a screening intravenous pyelogram and in some cases a voiding cystogram as well. New developments in localizing infection to the kidney or bladder and follow-up of patients with highly recurrent or persistent infection must be pursued. The problem is reminiscent of the relation between group A streptococcal infections and rheumatic fever. We feel impelled to treat streptococcal pharyngitis even though it is well recognized that only a small proportion of patients will be protected from rheumatic fever.

It seems to me, then, that studies on the natural history of urinary tract infections in females should be encouraged, with particular emphasis on defining those at high risk of developing complicated problems.

The other field to which I wish to direct attention is that of the urologic approach to urinary tract infections in females. The major contribution of the Stanford investigators has been their careful and detailed exploration of host factors leading to recurrent infection, evaluation of the indications and outcome of repair of vesico-ureteral reflux and dilation of the urethra, and description of a strategy for use of antimicrobial agents in treatment of recurrent infections. They are not alone in this. The views expressed in the articles published in this issue must be considered as part of a broad new consensus. One certainly gains this impression at national and regional meetings of the American Urological Association.

Nevertheless, it would be irresponsible of me not to point out that abuses still exist. Far too many unnecessary repeated cystoscopies, dilations of urethras, and repair of minimal grades of reflux are being done. Furthermore, some patients are receiving excessive or inadequate chemotherapy. It seems to me that each surgical, diagnostic and therapeutic procedure should be viewed, as are drugs, for both safety and efficacy, using study designs that would be acceptable by the same standard. The papers by the Stanford group clearly point out how this can be done.

CALVIN M. KUNIN, MD
Department of Medicine
University of Wisconsin, and
Medical Service, Veterans Administration Hospital
Madison

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Emergency Medicine

EMERGENCY MEDICINE gives every indication of being a rising star in the firmament of medical practice. Like its immediate predecessor over the horizon—family practice—it is broadly based and draws from among specialties. Both emergency medicine and family practice reflect a swing of the pendulum away from the narrow "vertical" organ system specialties and subspecialties toward a broader more "horizontal" capability to deal with a whole patient. It is worth noting that while family practice focuses on comprehensive and continuing care for a whole patient or a whole family, emergency medicine addresses the whole gamut of patients needing or seeking emergency care, but offers only episodic care in emergent situations where the usual definitive comprehensive or specialty care is not immediately available. This may be in the emergency treatment room of an urban hospital or it may be in a remote place. Both were spawned from general practice.

The advent of emergency medicine has produced much the same sort of critical and negative reactions as did the advent of family practice a few years ago, and for many of the same reasons. In addition there is a certain amount of semantic confusion about the term itself. To some it means the kind of emergencies which occur in a hospital setting and which appropriately are the responsibility of the various specialties in the hospital. To some others it means something like disaster medicine. Yet others consider it to be the immediate care which must be given when medical, surgical or psychiatric emergencies occur in places remote from where definitive care is given. And then there is the kind of care rendered in the emergency rooms or the emergency treatment rooms of hospitals—care for the walk-ins, the drive-ins and the carry-ins. These represent either real emergencies, or equally important, they are emergencies in the minds of those who come seeking help. This episodic, immediate and temporary care, wherever rendered, appears to be the subject matter of the rising specialty of emergency medicine.

This new specialty seems to have a true place in the firmament of modern medicine. There is a need and a demand for quicker and better treatment of medical emergencies, whether these be accidents from the highways, a painful belly or chest, a drug overdose, or a fear in the heart of a father who comes home to find his two-year-old child has a fever and is beginning to wheeze. It is such patients who appear in the treatment rooms of hospitals, large and small. No traditional specialist is trained to care competently for them all —nor is the family physician.

It appears that emergency medicine can and will fill this gap in medical practice.

—MSMW

Human Gut Microecology

THE PARTICIPANTS of the UCLA Interdepartmental Clinical Case Conference are to be complimented on the timely and accurate information presented elsewhere in these pages concerning the clinical aspects of gastrointestinal bacteriology.[1] During the past decade great interest has been aroused in this field. Pioneering work on the autochronous flora was performed by René Dubois and colleagues.[2] In addition, great advances in anaerobic technology were first stimulated by Hungate and, most recently, by the tedious taxonomic studies performed at the Virginia Polytechnic Institute Anaerobe Laboratory under the direction of Drs. Moore and Holdeman.[3] Increasing interest in the importance of the flora to gastrointestinal physiology was demonstrated in several recent symposia.[4,5]

The greatest limitation in gathering information on the gut flora has been the difficulty in developing simple bacteriologic methods for obtaining reproducible results, and the rapidity of changes in bacteriologic techniques. A clear example of this is my publication, in 1968, of what I thought to be a standardization of methods for identification and culture of the intestinal microflora in man. It grew obsolete within four years. Another example of the difficulty in correlating clinical material is demonstrated in this most recent review from UCLA. Studies analyzed on subphrenic abcesses were performed without detailed anaerobic methods, whereas the studies analyzed on aspiration pneumonia were done with a gas pack anaerobic technique. However, analysis of stools to evaluate diet and cancer epidemiologic factors was done with the most recent strict anaerobic techniques as defined by Finegold to be accomplished by either a glove box or roll tube. At present, either some modification of the techniques defined by Finegold or those defined by Moore must be used to obtain useful information. When these methods are used, studies become so laborious it requires a massive laboratory effort to perform any useful human research evaluations. Consequently, the entire research field becomes restricted because of the tedious technique. This point cannot be too strongly emphasized. Information will be limited until there is some technologic breakthrough which will yield methods that can be employed at less cost and be available to a wider range of investigators. However, the interest that has been aroused in this field and the rapid change in the techniques during the past three years do presage that the breakthrough is near. Better understanding of the clinical role of the gut microflora will evolve as studies turn up information about the factors that control normal and abnormal bacteria of the gut.

At birth the gut is relatively sterile except for occasional organisms that can be cultured from meconium. The colonization of the gut then varies, depending upon the type of diet the infant is fed. The feeding of human milk results in colonizing the gut differently than cows' milk or synthetic formulas. However, there have been no recent studies employing the above mentioned anaerobic techniques. Following colonization of the human gut, the so-called "adult type" microflora gradually develops as a regular diet is eaten. Most recent studies indicate that diet affects the quantitative and qualitative aspects of the microflora. But these studies are very limited. They have not been reproduced as yet, and, as is pointed out in the UCLA Conference, tedious identifications reveal a great number of unclassified organisms. The technologic limitation to identifying all of them leaves the statistical significance of the studies totally open to question. One cannot compare unidentifiable organisms. Using less fastidious anaerobic methods, Zubrzycki and Spaulding[6] did demonstrate a definite stability of the normal fecal flora in individual subjects. However, at the time their work was done, their techniques were very limited. As was indicated above, until techniques are simplified for identification of anaerobes, the exact influence of diet on the microflora will not be defined. Epidemiologic studies on high and low risk colon cancer and colon diverticular disease patients indicate that the diet has some relationship to the flora. Once again, the statistical significance of these flora variations is still open to question, due to the inability to completely qualitate bacteria.

Factors that appear to control normal bacterial populations as well as pathogenic bacterial growth within the lumen of the gut are of prime clinical

significance. Factors involved in controlling the microflora of the mouth are poorly understood. The mouth flora exhibit tremendous variation, depending on the host and the state of oral health. Also, little is known about conditions within the esophagus. Although bacteria have been noted within the esophageal mucosa during acute and chronic inflammatory disease, there have been no detailed quantitative or qualitative studies on the autochronous flora of the esophagus. When one reaches the stomach, evidence has clearly evolved to demonstrate that bacterial growth is related to the acid content and H^+ productivity of the gastric mucosa. At a pH of less than 2, the stomach is virtually free of bacterial growth. As the pH rises above 3, a rich flora can be recovered.[7] Duodenal and proximal jejunal bacterial studies also show an excellent correlation with gastric acid productivity. This indicates that the gastric acid barrier is effective in keeping down bacterial growth in the proximal small bowel. The reasons for control of the normal bacterial populations and of pathogenic bacteria become more complex as the bacterial flora develops in complexity in the ileum, and becomes very rich in the colon. Normal peristalsis and morphologic continuity of bowel are key factors which have been demonstrated to be important in controlling bacteria within the small bowel lumen. Stasis, obstruction, resection or a blind loop can cause bacterial proliferation higher in the small bowel than usual.

Biochemical factors reported in the past to have a role in controlling bacterial growth are mucus, lysozyme, colicin and fatty acids. Most recently, simple bile acids have been demonstrated *in vitro* to control intestinal bacterial growth.[8] Fiber in the diet has been postulated to possibly bind bacteria and control bacterial populations. Immunologic relationships between the host intestinal wall and the lumenal bacteria are of great interest. Persons deficient in immunoglobulin production have variations in their intestinal flora when compared with normal persons.[9] Most recent studies point out the mechanical activity existing between antigens and antibodies within the lumen. Of particular note is the work of Jones and Rutter. They have shown that the enteropathogenic effect of the K88 antigen of Escherichia coli can be decreased by neutralizing its adhesive properties.[10] Study of this type of physical effect on antigens should produce important results in understanding the control of both healthy bacterial populations and disease-producing organisms. Although the role of the majority of antibodies produced in the wall of the gut and their possible role in the lumen is not known at present, information in this field should prove of great clinical value in future years.

Finally of keen interest is the clinical significance of infections caused by multiple organisms, as is pointed out by Bartlett and Gorbach in the UCLA Specialty Conference here under discussion. There is no question that bacteria living together produce metabolic effects which either enhance or inhibit the growth of their colleagues. These particular phenomena have best been studied in the rumen of the cow, and most recently *in vitro* by Wolin and colleagues.[11] They add several organisms to a model *in vitro* ecosystem which includes continuous addition of growth nutrient factors, continuous study of metabolic by-products and repeated bacterial counts. Results of such studies reveal that there are definite interrelationships between multiple organisms. By varying the amount of nutrients, one can vary the type of bacterial growth. By varying the type of bacteria present, one can vary bacterial by-products such as fatty acids and possibly toxins. At present we have no model ecosystem of the human small or large intestine. Development of such a model could yield valuable information to help in the assessment of multiple infections in man, and the subsequent antibiotic or chemotherapeutic treatment.

MARTIN H. FLOCH, MS, MD
Departments of Internal Medicine
Norwalk Hospital, Norwalk Connecticut
Yale University School of Medicine
New Haven, Connecticut

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Thyroid Nodules and Thyroid Cancer

THE PROPER MANAGEMENT of thyroid nodules is still a hotly-debated issue. Single thyroid nodules occur in an estimated 2 to 4 percent of people living in non-endemic goiter areas in the United States. Some percentage of people with thyroid nodules will have thyroid cancer, the proportion being highest with the so-called "cold" nodules which accumulate radioiodine poorly compared to the paranodular tissue. This seems reasonable since most thyroid malignancies do not efficiently concentrate iodine or synthesize thyroid hormones. However, the problem remains that in a population of 1 million, between 20,000 and 40,000 people will have single thyroid nodules, of which approximately half are "cold" on scanning. Yet there will be only five deaths per year from thyroid cancer in this same population.[1] Routine removal of all thyroid nodules as a prophylactic measure thus seems unreasonable since the expected morbidity and mortality from the thyroid operation, not to mention the expense, would be greater than the expected ravages of untreated thyroid cancer itself. But therapeutic nihilism also seems unwarranted since "prophylactic" operation in patients with the highest risk of thyroid cancer should have much better odds. Clearly, the issue at hand is how best to identify the subpopulation at highest risk.

In the current issue of this journal, Greenspan has outlined his method for choosing high-risk patients. This consists of an initial screening from the history, physical examination and scan, with immediate surgical operation for those with highly suspicious thyroid enlargement. Operations in other patients are reserved for those whose thyroid enlargement does not regress with suppressive doses of thyroxine. Thirty percent of the patients operated on had thyroid cancer, making it 9.5 percent of his total study group with thyroid malignancy. His report suggests that thyroid cancer is several hundred times more common in patients with nodular goiter than epidemiologic data indicate.

Unfortunately, there are several important questions which are not answered by Greenspan's study. Perhaps the most important is the relation of the histologic diagnosis to biologic behavior of the lesions, particularly in the papillary and follicular carcinomas. There is considerable disagreement on the criteria to be used for making a diagnosis of thyroid malignancy. Even the same expert pathologist has been known to give different opinions on viewing the same histologic section at different times. The overwhelming majority of people with papillary or follicular thyroid carcinoma do not have further morbidity from their disease once it has been diagnosed. Those who die from thyroid cancer have almost invariably been operated on previously. Many do not have single thyroid nodules when first seen. Of those patients with goiter or single thyroid nodules who are not operated on, how many go to their grave harboring histologically malignant, yet biologically benign, thyroid cancers? According to an autopsy study at the Mayo Clinic,[2] 4 percent of patients without clinical evidence of thyroid disease who died from other causes had histologic thyroid cancer. This was approximately the same incidence as in their surgically treated patients with clinically palpable thyroid nodules. Thus, while Greenspan's method for selecting surgical cases apparently increases the yield of histologic cancer, it is not clear that it identifies those patients with high biologic risk.

What is the evidence that patients treated with surgical excision of thyroid carcinoma fare better than those not so treated? Controlled studies which might provide the answer to this question do not exist. However, Vander et al followed 218 unselected patients with non-toxic single thyroid nodules for 15 years.[3] None developed clinically evident thyroid cancer. Slight as they are, the risks from thyroid surgery may be greater than the risks from thyroid cancer, even in patients selected by Greenspan's criteria.

Our own plan of selection at the University of Oregon Medical School is somewhat different.[4] Our experience has not been quite as favorable as Greenspan's in the number of patients with multinodular goiter or single nodules whose lumps regress with thyroid hormone therapy. We therefore recommend excision only in those patients whose thyroids are very suspicious of malignancy when we first see them or those in whom the thyroid enlargement progresses in spite of the patient's receiving adequate suppressive doses of thyroid hormone. Since approximately 50 percent of all nodules are "cold," this information from the scan is not important in our initial decision. If the enlarged tissue stays the same size without regressing, we do not recommend operation except for cos-

metic reasons. This considerably reduces the percentage of patients operated on compared with Greenspan's series, but apparently works just as well in screening for thyroid cancer. We have used this approach for over 25 years. None of our nonoperated patients has developed biologic malignancy to my knowledge.

MONTE A. GREER, MD
Professor of Medicine
Head, Division of Endocrinology
University of Oregon Medical School
Portland

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Patient Care Audit

PEER REVIEW ACTIVITIES in California and elsewhere have begun to focus on the patient care audit. Indeed the California Medical Association and the California Hospital Association have joined in a massive effort to introduce patient care audit into virtually every hospital in California. The model is similar to that developed by Clement Brown. This is being accomplished by training interdisciplinary teams from each hospital in the audit process by holding a series of workshops, following which each team returns to its own hospital and brings the message of medical audit to the medical staff and to the hospital administration.

The patient care or medical audit, as it is sometimes now called, is a first attempt on a major scale by the private sector to assess objectively the quality of patient care actually rendered in a practice setting, the hospital. It has already produced some substantial benefits. At the very least, it has convinced physicians on the medical staffs of hospitals, and hospital administrators who are trying to maintain quality and balance the hospital budgets, that an assessment of the quality of the care being rendered in the institution is both important and useful.

The genius of the technique being used, which makes it acceptable to the professionals concerned and gets results, is that the criteria are chosen and the compliance performance required are determined by the medical staff and other professionals whose performance is to be assessed. This clearly focuses on the local situation, challenges those most directly involved, and even respects the doctor-patient relationship. Contrary to what some might have expected, experience has shown that these self-imposed standards tend to be high, and when they are not met, this becomes a matter of professional concern and effective corrective action is usually taken.

It is proper and as it should be that medicine assess its own professional performance and be accountable to the public. There has always been some form of peer accountability in the tradition of medicine. This should and will continue, with or without government mandate. In fact no one else can really do it. Public accountability is also not new. It was a part of the Code of Hammurabi, and it is just as real a concern today, although perhaps not quite so brutal. The report elsewhere in this issue by Barbour, Lambert and Fisher reflects a step forward in the direction of public accountability in patient care which is so necessary for American medicine in these times.

—MSMW

The Fascinations and Frustrations of Diabetes Mellitus

ONE HUNDRED YEARS AGO, Bouchardat, professor of public health in Paris, published a compilation of his observations on diabetes extending over a 35-year period. In this book he subdivided the diabetic state in man into (a) the severe "pancreatic" type; (b) the "fat" diabetes of moderate glycosuria, associated with overweight and hyperuricemia and (c) the "nervous" diabetes which did not fit the first two classifications.

He pointed out that the pancreatic form led to rapid weight loss, cachexia and death. No effective therapy was known. However, for the obese, moderate group of diabetics he recommended and successfully used a regimen consisting of a diet low in calories and in soluble carbohydrates, coupled with a strict and consistent schedule of physical exercise. Most patients who adhered to this regime lived long and useful lives.

Let us examine what changes have occurred

since Bouchardat, what advances we can register in the understanding of diabetes and what progress has been made in treatment. On the positive side of the ledger we can list several points. We have now quite a detailed picture of intermediary metabolism of the foodstuffs and we understand that in diabetes, because of an absolute or relative lack of insulin, all metabolism is tipped to the side of breakdown. This is so because insulin is the hormone of storage, of build-up, of anabolism. When that side of the balance is weak, then the effect of catabolic factors (glucagon, adrenaline, corticoids) predominates. But it is still difficult for us to understand why it is that moderate, non-ketotic obese diabetics should retain and maintain excess weight.

We have, over the past hundred years, detected and isolated almost all the hormonal factors which regulate metabolic pathways. We know their chemical structure, including the three-dimensional morphology. We measure them accurately at incredibly small concentrations. Yet we still remain ignorant of the accurate molecular basis of almost all hormonal actions. We have learned to understand the regulation of hormonal secretions by feedback mechanisms, and the beta cell has been explored at rest and in action most carefully and minutely. But we do not understand the familial or genetic defect which leads to faulty, inadequate or distorted regulation of insulin secretion in human diabetes.

The biggest advance came 53 years ago with the discovery of insulin. The type of patients for whom Bouchardat, Naunyn, Minkowski could do nothing are today doing well indeed (at least for 15 to 25 years) on daily insulin, controlled diet and so forth. But, as we well know, the effect of the diabetic state on the blood vessels (large and small) and on the peripheral nerves (voluntary and autonomic) leads to invalidism, suffering and premature death in many. We cannot and should not rest until we can understand and prevent retinopathy, nephropathy, neuropathy and the advanced atherosclerosis of diabetes. These are difficult problems. Their solution will throw light on non-diabetic vascular and nerve diseases, as well as on diabetes itself.

Conferences, such as the Kroc meeting summarized admirably by McMillan in the October issue [McMillan DE, Amacher P: Conference on the pathophysiology of diabetes mellitus. West J Med 121:350-355, Oct 1974], serve to bring together workers from many disciplines to discuss and aid each other in the elucidation of seemingly minor points. All these "little" advances add up over the years into palpable progress. McMillan remarks, in the last sentence of his report, on "the growing diversity of approaches utilized by investigators in their efforts to improve our understanding of diabetes." He is of course correct. That there is a diversity of approaches is due to the fact that diabetes affects the cellular metabolic processes in every organ and disturbs a great variety of functions. This is why we are at once fascinated and frustrated in studying the protean manifestations of this disease.

RACHMIEL LEVINE, MD
Medical Director and
Director of Metabolism Department
City of Hope Medical Center
Duarte, California

CASE REPORTS

Refer to: Ackerman WJ: Stupor, bradycardia, nypotension and hypothermia—A presentation of Wernicke's encephalopathy with rapid response to thiamine. West J Med 121:428-429, Nov 1974

Stupor, Bradycardia, Hypotension and Hypothermia

A Presentation of Wernicke's Encephalopathy with Rapid Response to Thiamine

WILLIAM J. ACKERMAN, MD
San Diego

THE PRESENTATION of a stuporous, hypothermic alcoholic patient in the emergency ward is not uncommon. Initial considerations include environmental exposure, sepsis, and endocrinopathy. This report describes such a presentation as a manifestation of Wernicke's encephalopathy.

Report of a Case

A 73-year-old man was brought to University Hospital, San Diego, July 26, 1973, with a history of having been found unresponsive on the floor of his hotel room. At the time of his arrival in the emergency ward, the temperature in San Diego was 79°F. The patient's son stated that his father drank six to ten cans of beer a day and had maintained a marginal diet for many years. The patient was obtunded, with vital signs as follows: a blood pressure of 80/60 mm of mercury, pulse rate of 45 per min., rectal temperature of 90°F, and Cheyne-Stokes respirations. The patient was thin and disheveled, with dry mucous membranes and poor skin turgor. On neurological examination he responded to pain only with retraction of all extremities. Bilateral sixth nerve palsies, and bilateral horizontal nystagmus on limited lateral gaze were noted. The pupils were midposition, and they reacted sluggishly, but symmetrically, to light. No abnormality was seen on funduoscopic examination.

Initial laboratory data included hematocrit of 37 percent, hemoglobin of 11.8 grams per 100 ml, leukocyte count of 7,200 per cu mm, blood glucose of 106 mg, urea nitrogen of 53 mg and creatinine of 3.4 mg per 100 ml. Serum electrolytes were normal. SGOT was 167 units, LDH 163 international units, CPK 980 international units, serum cortisol 16.5 mcg, and total thyroxine 2.9 mcg per 100 ml, with a free thyroxine index of 4.5.

Urine osmolality was 479 mOs, with an unremarkable urine sediment. Cerebral spinal fluid analysis was normal. Blood gas analysis showed a moderate respiratory alkalosis. Results of toxicologic studies (including alcohol) and cultures of blood, sputum, urine, and cerebrospinal fluid were unremarkable. Chest and skull roentgenographs were normal. An electrocardiogram showed a sinus rate of 50 with no other abnormalities.

The patient was treated with a warming blanket, intravenous fluids (5 percent dextrose and half normal saline solution), 200 mg of thiamine intramuscularly, initially, and then 300 mg daily by mouth. No antibiotics, thyroid preparations, or corticosteroids were given. Within 24 hours the patient was alert and sitting in a chair. Rectal temperature was 97.7°F, blood pressure was 100/60 mm of mercury and pulse rate was 60 per minute. Examination at that point showed a disoriented, ataxic male without evidence of ocular palsies or nystagmus. With continued hydration the blood urea nitrogen and creatinine returned to normal on the fifth hospital day.

Comment

In this patient, hypothermia was not secondary to exposure, sepsis, or myxedema. (Total thyroxine was low, tetrathyroxine index was normal.) A recent review of 245 cases of Wernicke-Korsakoff syndrome by Victor, Adams, and Collins,[1] described the presentation of stupor or coma as uncommon (4 percent and 1 percent of cases,

From the Department of Medicine, University Hospital of San Diego County, San Diego.

Submitted March 1, 1974.

Reprint requests to: W. J. Ackerman, MD, Department of Medicine, University Hospital of San Diego County, 225 West Dickinson Street, San Diego, CA 92103.

TABLE 1.—*Reported Cases of Wernicke's Encephalopathy and Hypothermia*[1] *(Cases Since 1945)*

Author	*Cases*	*Presentation*	*Temp (°F)*	*Pulse Rate*	*Blood Pressure*	*Thiamine*	*Course*
Rosenblum[4]	1	disoriented	95	..	80/60	yes	died
Koeppen[2]	1	unresponsive	87	60	60/—	no	died
Victor[1]*	1	unresponsive	92	..	..	yes	recovered
Philip[9]	3A	disoriented	85	50	110/80	no	died
	B	confused	94	..	..	yes	recovered
	C	stupor	90	..	..	no	died
Ackerman†	1	stupor	90	45	80/60	yes	recovered

*Also reported one case with temperature 97.0°F.
†Present case.

respectively). Hypothermia and hypotension were rare (1 percent and 2 percent of cases). Bradycardia was not mentioned. Only the patient described by Koeppen and coworkers[2] presented with the same features: stupor, bradycardia, hypotension, and hypothermia. Their patient was given glucose solutions intravenously without previous administration of thiamine, a situation that may be hazardous in the presence of depleted thiamine stores.[3] Seven reported cases of Wernicke's encephalopathy and hypothermia (95°F or less) are listed in the table. Of four patients treated with thiamine, three survived; of three not treated with thiamine, all died. The treated patient who did not survive (Rosenblum and Feigin[4]) was not given thiamine until the second hospital day, when bilateral paralysis of the medial rectus muscles was noted.

There is adequate experimental[5,6] and clinical[7,8] evidence to show the hypothalamus plays a major role in the regulation of body temperature. In the three cases reported by Philip and Smith,[9] lesions were noted in the posterior, or posterior and lateral hypothalmus. (One patient died of carcinoma of the stomach 15 months after discharge.) The posterior hypothalamus is sensitive to lowered blood temperature, and initiates heat production and heat conservation mechanisms.[10] This area was involved in 6 of 32 cases in the series reported by Victor et al.[1] Experimental studies[11,12] suggest that the hypothalamus is also concerned with regulation of blood pressure. In cases of Wernicke's encephalopathy and hypotension, it is not always clear whether the hypotension is due to hypovolemia, a hypothalamic lesion, or other causes. Postural hypotension was present in 32 of 40 patients with Wernicke's disease studied by Birchfield,[13] who postulated involvement of the efferent sympathetic nervous system. Despite dehydration, hypotension, and lack of evidence of heart disease, our patient presented with bradycardia. Experimentally, hypothalamic stimulation will cause an increase in heart rate,[14] and theoretically an ablative lesion would produce bradycardia. In rats, bradycardia is a constant feature of severe thiamine deficiency.[15] In the present case, hypothermia is an alternative explanation for the bradycardia.

Summary

A case of extreme presentation of Wernicke's encephalopathy is described. Evidence presented suggests that hypothermia, and perhaps bradycardia and hypotension, represent hypothalamic involvement in Wernicke's encephalopathy. The high mortality rate in untreated patients and the benignity of the therapy suggest that parenteral thiamine should be a part of the initial management of all patients with this clinical picture. The hazards of intervenous therapy with glucose solutions in the presence of thiamine deficiency is emphasized.

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Refer to: Noe JM, Barber J: Chronic leg ulceration in a patient with leprosy. West J Med 121:430-432, Nov 1974

Chronic Leg Ulceration in a Patient with Leprosy

JOEL M. NOE, MD
Stanford

JOAN BARBER, MD
San Jose

WHILE THERE ARE a reputed fifteen million cases of leprosy in the world, the diagnosis is often missed in the United States. This is due partially to its rarity, but also to its many unusual and confusing presentations. There are approximately one hundred newly diagnosed cases reported per year in the United States, the largest number of these being from California (about 26 new cases each year) with about one-third of the patients being Mexican in origin.[1]

We recently saw a case of leprosy in a 45-year-old Cuban immigrant who presented with chronic leg ulcers.

Report of a Case

The patient was a 45-year-old Cuban woman who presented in June 1973 with ulcerations and anesthesia of the left lower leg of about six months' duration. She had recently arrived from Spain after having gone there three years previously from Cuba. She had been seen by a physician in Spain because of a skin rash that developed early in 1972 and a sulfa drug had been prescribed for her in December 1972. In February of 1973 the rash worsened and ulcers developed on the left leg. Because she felt this might be a reaction to the sulfa drug, she stopped taking it. At the time she was examined by us, information as to the type of "sulfa" drug and the cause and treatment of the "skin rash" was unattainable.

The patient described the rash as having started as small pink non-pruritic areas on the arms and legs which later became brownish and spread to her face. The ulcers on the legs began as large erythematous areas which subsequently blistered and then sloughed, leaving deep ulcerations. There was no known family history of a similar disease process.

Figure 1.—A well-circumscribed, flat, erythematous macule on palm of hand.

On physical examination the patient was afebrile and the vital signs were stable. There was no loss of eyebrows nor was there any infiltration of the skin of the face. The eyes, ears, nose, and throat were normal without nodules or ulcerations. There were several 1-cm circumscribed, flat, erythematous lesions over the lower jaw and chin. Results of thoracic, cardiac, and abdominal examinations were within normal limits. There were multiple well-circumscribed, flat reddish-brown macules over the skin of the extremities and upper back (Figure 1). These varied from 1 to 5 cm in diameter and were uniformly hypasthetic to pinprick.

The skin of the lower extremities was very thin and it was anesthetic in the area consistent with the sensory distribution of the cutaneous branches of the left common peroneal nerve. Within the distribution of this nerve there were also noted to be deep, circumscribed, irregular, infected ulcers varying from 0.5 cm to 8 cm in diameter with deep interconnecting sinuses extending as deep as the underlying muscular fascia (Figure 2). Mild weakness of the dorsiflexors and plantar everters of the left foot was noted. In addition the left

From the Department of Surgery, Stanford University Medical Center (Dr. Noe); and the Department of Medicine, Santa Clara Valley Medical Center (Dr. Barber).

Submitted April 29, 1974.

Reprint requests to: J M. Noe, MD, Department of Surgery, Stanford University Medical Center, Stanford, CA 94305.

Figure 2.—Chronic leg ulcerations.

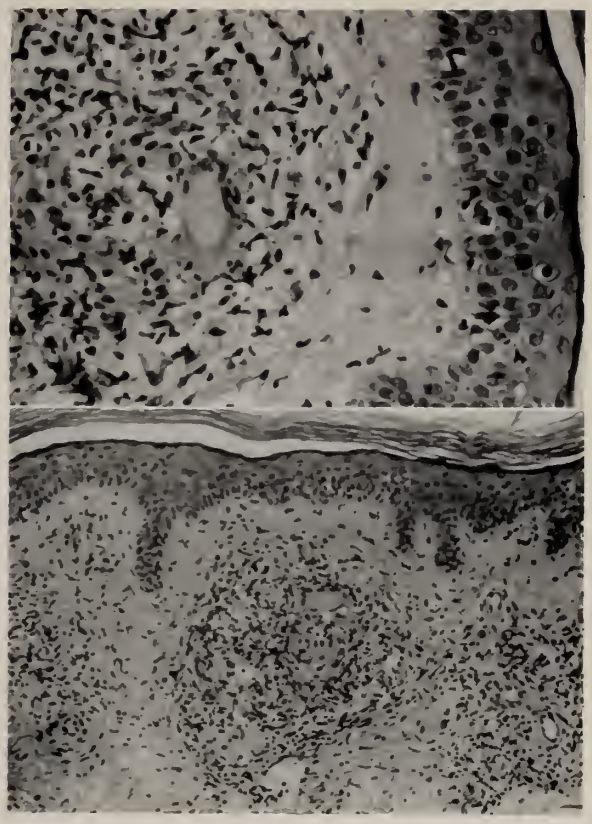

Figure 3.—Biopsy specimen from margin of an ulcer, showing non-caseating granulomas with giant cells, epithelioid histiocytes and foamy histiocytes. (Upper frame ×400, lower frame ×80.)

common peroneal nerve at the knee was palpable. All arterial pulses were present, normal and equal. There was no evidence of venous or arterial disease. Deep tendon reflexes were normal.

Laboratory data

The hematocrit was 34 percent, leukocyte count 5,500 per cu mm with the cell differential normal, fasting blood glucose 90 and two-hour post-prandial blood sugar 132. Serologic tests for syphilis were negative. Cultures from the ulcers grew enterobacter cloacae and staphylococcus aureus. The cultures were negative for fungus and mycobacterium tuberculosis. X-ray films of the bones of the lower extremities gave no evidence of osteomyelitis. Nerve conduction studies of the left peroneal nerve compared with the right showed extremely long latency with pronounced slowing of nerve conduction. Nerve conduction in the arms was supra-normal.

A biopsy specimen obtained from the margin of one of the ulcers showed multiple areas of non-caseating granulomas with giant cells, epithelioid histiocytes and foamy histiocytes. These were tightly arranged in perivascular granulomas (Figure 3). A sural nerve biopsy showed very similar granulomatous changes with considerable infiltration of the sural nerve, but neither biopsy showed lepra bacilli with Fite's stain.

It was eventually learned that the sulfa drug taken for the skin rash was dapsone (Avlosulfon®) and that it had been given by the physician who treated the patient for the diagnosis of leprosy. Unfortunately, the patient had not understood the nature of her disease.

On the basis of the history, clinical examination, and laboratory data, a diagnosis of leprosy was made and dapsone was again prescribed, 50 mg by mouth four times a day.

The ulcers, treated initially with local wound care, were successfully closed with thin split-thickness skin grafts. The patient then was able to ambulate with an unna boot protecting the relatively anesthetic left leg from trauma. After the wounds had healed, and with the patient ambulating, she was discharged, taking dapsone.

TABLE 1.—*Etiology of Chronic Leg Ulceration*[5]

Vascular
- a. Arterial: large vessel; small vessel; acute vasculitis
- b. Venous: stasis; post phlebitic syndrome
- c. Lymphatic: congenital, acquired

Neoplastic
- Squamous cell carcinoma, basal cell carcinoma, malignant melanoma, Kaposi's sarcoma

Traumatic

Infectious
- a. Bacterial
- b. Mycotic: blastomycosis, leishmaniasis
- c. Syphilis
- d. Chronic osteomyelitis
- e. Tuberculosis
- f. Other: Meleney's ulcer, cat-scratch disease, Buruli ulcer

Metabolic
- a. Necrobiosis lipoidica diabeticorum, erythema induratum, Sjögren's disease
- b. Hyperimmune states: pyoderma, pyoderma gangrenosum
- c. Blood diseases: Cooley's and sickle cell anemias, cryoglobulinemia, leukemia, senile purpuras

Neurotrophic
- a. Central lesions: tabes dorsalis, syringomyelia, maldevelopment of cord, pressure sores
- b. Peripheral nerve lesions: diabetes, trauma, leprosy, avitaminosis, amyloid, heavy metals

Discussion

Leprosy is a chronic, slowly progressive granulomatous disease caused by the acid-fast bacillus mycobacterium leprae. Its multitude of different presentations is owing mainly to differing degrees of host resistance. At one end of the spectrum is lepromatous leprosy in which there is little host resistance and the bacilli invade skin, nerves and mucous membranes diffusely, as well as commonly involving internal organs.[2] Pathologically, foam cell granulomas infiltrate the tissues, and grossly the skin is thickened and nodular. Eventually the classical "leonine facies" may develop. At the other end of the spectrum is tuberculoid leprosy with higher degrees of host resistance and only focal involvement of nerves and areas of skin. The skin lesions are much more subtle, usually being only flat, circumscribed hypopigmented or hyperpigmented plaques. Biopsy of these lesions shows the typical giant cells and epithelioid cells of tuberculoid granulomas. Common to the entire spectrum of leprosy is the unique involvement of the nerves. Both the large peripheral nerves—first the sensory fibers and later the motor fibers—as well as the small sensory nerves underlying the skin lesions are commonly involved. A careful neurologic examination may uncover important clues to the diagnosis since no other infectious disease and very few dermatologic conditions involve the peripheral nerves in this way. Skin ulcerations may occur in at least two ways. The anesthetized areas of the skin are easily traumatized, burned or secondarily infected. In addition, patients with diffuse lepromatosis may develop an acute immune-like reaction known as "erythema necroticans," in which angular inflamed lesions develop over the legs or arms or both, and then shortly slough to leave deep ulcers.[3,4]

In the differential diagnosis of chronic leg ulceration (Table 1) a combination of (1) travel in or history of living in an endemic area and (2) a peripheral nerve lesion with or without associated anesthetic areas, and (3) suggestive skin lesions in the distribution of the involved nerve, should make one suspicious of leprosy.

The patient presented had lived in Cuba and she had a peripheral nerve lesion associated with skin lesions in the distribution of the involved nerve—in her case it was the common peroneal—with anesthesia consistent with the cutaneous branches and disability of motor function consistent with the superficial peroneal nerve branch.

We have presented this unusual case as a reminder to the practicing clinician that leprosy still exists in the United States and continues to evade diagnosis. We would like to emphasize that culturing bacterial pathogens found superficially may not be sufficient and that skin and nerve biopsy may be necessary to make the correct diagnosis of leprosy. It is a treatable infectious disease that will only be discovered if suspected and looked for on a biopsy.

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LETTERS *to the Editor*

Twelve-Year Survival of a Patient with Letterer-Siwe's Disease

To the Editor: In 1962, a 1-year-old girl became severely ill with what soon proved to be Letterer-Siwe's disease. I treated the child with continuous cortisone for five and one-half years, and she remains well and free of any residual of disease six years later, at age 13. There were no growth disturbances or other complications of cortisone therapy.

The disease, which was confirmed by cervical lymph node biopsy, was manifested by profound anemia of 4.5 grams hemoglobin, fever, gross adenopathy, hepato- and splenomegaly, skin rash and multiple osteolytic lesions in skull and long bones. Later, she developed diabetes insipidus, which did not respond to pituitary irradiation, but was kept in clinical improvement by injections of pitressin tannate, until it disappeared with cure of her basic disease.

The only treatment was oral cortisone in the form of prednisone the first month, starting at 80 mg and decreasing to 24 mg of methylprednisolone after one month, then decreasing gradually to 4 mg of methylprednisolone six months later; a temporary increase to 24 mg was necessary in October 1963 with gradual tapering so that from May 1965 to January 1966 she was on 0.9 mg of betamethasone (1½ tablets) daily.

In July 1967 she was on three tablets of Celestone® (betamethasone) daily, decreasing to two daily by October 1967, and stopping completely in March 1968.

Other agents were not used. There were some exacerbations and remissions paralleling dosage changes. There were no permanent sequelae of steroid therapy, and growth was normal. On August 30, 1974, her weight was 126 pounds and height 60¼ inches. X-rays at that time showed no residual of the former lytic lesions in skull, chest, pelvis or femurs. She had been reported to have had some hearing difficulty, but the evidence was sketchy.

Pathological diagnosis was made on the cervical lymph node biopsy by the pathology department of O'Connor Hospital of San Jose, California, and confirmed 12 years later by the Pathology Department of Stanford University Medical Center.

I realize the pitfalls of single case observations, and the reported occurrence of spontaneous remissions. I feel this case is worth bringing to print because of the 6-year length of cure, and the fact of "pure" treatment with cortisone, purposely avoiding the current practice of alternate day therapy.

The pediatric consultant was Dr. Karl Robinson.

William W. Johnson, MD
Los Gatos, California

Organ Ischemia

To the Editor: I would like to compliment Dr. R. L. Jamison for his excellent review of "The Role of Cellular Swelling in the Pathogenesis of Organ Ischemia," which was recently published in the Medical Progress section (West J Med 120: 205-218, Mar 1974). He has accurately detailed many of the current concepts regarding the importance of cellular swelling with regard to the etiology and perpetuation of organ ischemia. We are indebted to him for this timely review.

However, he has not included data regarding experimental work which we have performed and have recently reported, concerning the preservation of canine kidneys with a cold hyperosmolar intracellular electrolyte-type perfusate (Sacks SA, Petritsch PH, Kaufman JJ: Canine kidney preservation using a new perfusate. Lancet 2:1024, May, 1973). In that paper, we espoused many of the theories upon which Dr. Jamison has elaborated. We thoroughly agree with Dr. Jamison regarding the validity and application of these theories.

In addition to having omitted our experimental work, Dr. Jamison stated, in effect, that Collins' solution is "hyperosmotic" (pg. 215, para. 1).

Collins' solution is, in fact, an intracellular electrolyte-type solution which is iso-osmotic and, as such, does not have the capacity to prevent the movement of water into ischemic cells. We were able to remedy this physico-chemical malady by rendering a similar intracellular electrolyte solution hyperosmolar upon the addition of mannitol. By altering the intracellular electrolyte composition of Collins' basic solution, and by rendering the solution hyperosmolar upon the addition of mannitol, we have been able to preserve canine kidneys for 48 and 72 hours by initial perfusion and hypothermic storage.

We feel that Dr. Jamison should be aware of these data.

We would again like to thank him for his complete review of a difficult subject, and for the meaningful experimental contributions which he has made.

STEPHEN A. SACKS, MD
Division of Urology
Department of Surgery
University of California
Los Angeles

* * *

The Author Replies

I thank Dr. Sacks for his comments and apologize for not including a reference to his excellent work, of which I was indeed aware. However, I did not intend the list of references in my review to be comprehensive and thought several points made by Sacks et al (Sacks SA, Petritsch PH, Kaufman JJ: Canine kidney preservation using a new perfusate. Lancet I:1024, 1973) were also made in the paper by Acquatella et al (Acquatella H, Pérez-González M, Morales JM, Whittembury G: Ionic and histological changes in the kidney after perfusion and storage for transplantation. Transplantation 14:480, 1972). Moreover, some reservations have been expressed by the latter authors (Whittembury G, González C, Acquatella H: Letter to the Editor. Lancet II:446, 1973) about the use of some constituents in the solution recommended by Sacks et al and Sacks has responded (Sacks SA: Letter to the Editor. Lancet II:622, 1973).

Collins et al (Collins GM, Bravo-Sugarman M, Terasaki PI: Kidney preservation for transportation. Lancet II:1219, 1969) refer to four different solutions, C_1 to C_4. The solution the authors recommend, C_4, is hyperosmotic, in the conventional meaning of the term, that is, having an osmolality significantly greater than that of plasma (which is approximately 290 mOsm/kg H_2O), although it is not nearly as hyperosmotic as the solutions used by Sacks et al.

REX L. JAMISON, MD
Department of Medicine
Stanford

Trauma Rounds

Chief Discussant
JULIAN HOFF, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Hoff J: Evaluation of the patient with head injury (Trauma Rounds). West J Med 121:435-438, Nov 1974

Evaluation of the Patient with Head Injury

RICHARD BRANAN, MD:* A 6-year-old girl was admitted to the San Francisco General Hospital after being struck by a car. On examination, she was unresponsive to commands, with intermittent agitation and purposeful movements of all four extremities. The blood pressure was 120/80 mm of mercury; the heart rate 100 beats per minute and respirations were rapid, deep and unobstructed. A contusion was present over the left brow. The lungs were clear and the abdomen was soft and flat. There was a compound fracture of the left femur.

During radiographic examination, the patient became progressively less responsive, with slowing of respirations. The trachea was intubated. A few minutes later, the right pupil became dilated, and the patient failed to respond to painful stimuli. She was transferred immediately to the operating room for exploratory burr holes. Enroute to surgery dexamethasone was given intravenously and a mannitol infusion was begun.

While operative preparations were being carried out, apnea ensued and the left pupil also became dilated. Burr holes were placed bilaterally at temporal, frontal and parieto-occipital sites. The exposed cortical surface was contused and swollen, but an extracerebral hematoma was not identified. During trephination, peritoneal lavage[1] revealed intra-abdominal bleeding, and a laparotomy was done. A ruptured spleen was removed. After all wounds were closed, cerebral arteriographic studies were done. The cerebral circulation was noticeably slowed, but a localized mass was not identified. After angiography the patient was returned to the operating room and the left femoral fracture was reduced and immobilized.

Postoperative care included administration of dexamethasone, intermittent administration of mannitol, systemic hypothermia (34 to 35°C) and ventilatory assistance as necessary. By the third day, the patient began to move spontaneously, the pupils were equal and responsive to light and respirations were normal. The next day the patient responded to commands and thereafter improved progressively. After four weeks she was discharged; a month later she returned to school. A year after the accident the patient showed neither physical nor psychological sequelae of her multiple injuries.

F. WILLIAM BLAISDELL, MD:† *Dr. Hoff, you were the attending surgeon in this case. Will you comment on the management of head injuries in general?*

JULIAN HOFF, MD:‡ The patient with a severe head injury should be managed initially in the

*Chief Resident, Neurosurgical Service, San Francisco General Hospital.

Sponsored by The American College of Surgeons Northern California Trauma Committee. Supported in part by NIH Grant GM18470.

Reprint requests to: D. D. Trunkey, MD, Department of Surgery, San Francisco General Hospital, San Francisco CA 94110.

†Chief of Surgical Service, San Francisco General Hospital; Professor of Surgery, University of California, San Francisco.

‡Chief of Neurosurgical Service, San Francisco General Hospital.

same way as all patients who sustain life-threatening trauma. First, the adequacy of the airway must be ensured and hemorrhage must be controlled. A thorough physical examination must follow, and basic resuscitation begun, usually including intravenous and bladder catheters, a nasogastric tube and often an endotracheal tube. If arterial hypotension is present, it is caused rarely, if ever, by head injury. Unsuspected bleeding originating in the chest, abdomen or an extremity is almost always responsible for shock. For this reason, I would completely concur with the decision to carry out peritoneal lavage and laparotomy. This was one of the key factors in the ultimate survival of this patient. Similarly, airway obstruction is not neurogenic and can usually be relieved by prompt tracheal intubation.

Patients with severe head injury are usually unconscious when first seen, but not always. When a patient's sensorium is abnormal, regardless of the presence or absence of obvious external signs of head injury, careful neurologic observation is essential. The most important neurologic sign we can evaluate is the patient's state of consciousness; impairment may range from subtle confusion to profound coma, often with changes from moment to moment.

Our approach to injured patients requiring neurological observation at San Francisco General Hospital is as follows. Examinations are brief and include assessment of: (1) level of consciousness; (2) movement of the extremities, either spontaneously by the patient or induced by the examiner and (3) brain stem reflexes. We rely heavily upon pupil size and responses to light, and on movement of the eyes during the doll's head maneuver, that is, the eyes remain fixed on a specific point despite rotation of the head. This maneuver tests the integrity of the brain stem. Cold caloric stimulation is used when the doll's head maneuver fails to move the globes. Corneal, gag and cough reflexes (usually elicited during endotracheal intubation if intact) provide additional evidence for or against the integrity of brain stem function. Deep tendon reflexes and Babinski signs are less reliable in patients with head injury than in other patients, although they may be helpful to lateralize an intracranial lesion.

Our neurological examination is kept brief, allowing us to repeat it often. By frequent and consistent repetitions we can then determine the course of the injury, something of its nature (for example, a right cerebral problem), what diagnostic aids to use and when to use them. I cannot emphasize too much the value of a repeated, brief and consistent examination.

Occasionally the patient's condition deteriorates precipitously. Our patient today is such a case. Clearly a tragic outcome seemed inevitable unless we could evacuate an intracranial clot (presumably on the right side because of the right pupil dilatation initially) or reduce the brain swelling without delay or both. Diagnostic studies were interrupted and the patient was taken directly to surgery for exploration. Simultaneously, drugs and ventilatory support were given to control brain swelling. When extradural and subdural hematomas were excluded by burr holes, angiographic studies were done to eliminate the possibility of a missed deep mass demanding surgical removal.

Usually the condition of a patient does not deteriorate so rapidly, and diagnostic studies can proceed in a more orderly fashion. In our hospital these studies commonly include: (1) chest x-ray films; (2) skull x-ray films; (3) cervical spine x-ray films and (4) cerebral arteriographic studies. The chest film is essential to assure us that an unsuspected chest injury is not overlooked. Hypoxia and hypercarbia, often sequelae of pneumothorax and hemothorax, add insult to the already injured brain. Skull films disclose fractures as well as occasional surprises, such as foreign bodies. Films of the cervical spine are necessary to exclude unsuspected fractures—in our experience about 3 percent of patients with severe head injuries have associated neck injuries. Cerebral arteriography is our diagnostic "trump card." Lesions can be identified with a high degree of accuracy, allowing us to plan our surgical approach with some precision. Three of every four patients who require operation for head injury at San Francisco General Hospital have angiographic studies done before operation.

We have not been satisfied with the reliability of echoencephalography nor with the practicality of electroencephalography as preoperative diagnostic tools. Similarly, air studies have limited diagnostic accuracy in acute trauma. Lumbar puncture is not done routinely because the information gained rarely influences our treatment plan.

A Physician: *How often do patients herniate from lumbar puncture when they have increased intracranial pressure?*

Dr. Hoff: Not often. When an intracranial mass is not present, as in the disease pseudotumor cere-

bri, almost never. When a mass is present, such as a subdural hematoma or a large brain tumor, herniation occurs often enough to justify our reluctance to tap. Occasionally a patient with no available history of injury arrives in the emergency room deeply comatose, with a high temperature and a stiff neck. The physician's dilemma is obvious: to tap or not to tap? Generally we prefer to do angiographic studies in this type of patient first, to exclude a mass, then do a lumbar tap later if no mass is found to exclude meningitis.

A PHYSICIAN: *Were there lateralizing signs in this patient to guide you in placing the burr holes?*

DR. HOFF: Yes. The right pupil dilated and became fixed to light, while the left remained normal until late. The doll's head maneuver confirmed the right oculomotor palsy, which was presumed to result from right uncal herniation. The first burr hole was placed in the right temporal region. In 80 percent of cases the dilated pupil correctly predicts the herniating side.

A PHYSICIAN: *How do you determine priorities in the patient with multiple injuries including a severe head injury?*

TABLE 1.—*Physical Signs Before Operation in 100 Patients with Subdural Hematoma*

Physical Signs	*Percent*
Level of consciousness:	
Alert	0
Stupor	79
Coma	21
Decerebrate posturing	34
Abnormal respirations	24
Hemiplegia	26
Unilateral fixed pupil dilatation	57
Bilateral fixed pupil dilatation	13
External sign of head trauma	92
Other major injuries	13

DR. HOFF: This is based simply upon the most obvious threat to the patient's life. Generally, severe abdominal or chest injuries demand the most urgent treatment. Head injuries, too, may require immediate operation. Sometimes craniotomy and laparotomy are done at the same time when the priorities are unclear, or delay of one or the other seems unwise.

A PHYSICIAN: *How helpful are the various neurological findings in ultimate prognosis?*

DR. HOFF: Approximately two years ago, we reviewed 100 cases of acute subdural hematoma at San Francisco General Hospital. The physical signs before operation shown in Table 1 were tabulated and were compared to survivors (25 patients) and nonsurvivors (75 patients) (Table 2). The likelihood of death was greater in the presence of fixed pupillary dilatation and all patients in shock at the first examination later died. A lucid interval, contrary to the experience of others, was more often associated with a fatal outcome (40 percent) than with recovery (28 percent).

Since that time we have been able to reduce our mortality rate further, to about 60 percent, by aggressive surgical intervention and treatment.

A PHYSICIAN: *How do you manage high intracranial pressure after head injury?*

DR. HOFF: Currently we reduce intracranial pressure medically in four ways: (1) with steroids—dexamethasone, 10 mg administered intravenously, then 5 to 10 mg administered every six hours intramuscularly for several days; (2) with osmotic diuretics—mannitol, 1.5 grams per kg of body weight administered intravenously every 24 hours,

TABLE 2.—*Preoperative Physical Signs in Survivors and Nonsurvivors of Patients Operated upon for Subdural Hematoma*

	Survivors (25 Patients)		*Nonsurvivors (75 Patients)*	
Preoperative Physical Signs	*Number of Patients*	*Percent*	*Number of Patients*	*Percent*
Stupor	20	80	59	78
Coma	5	20	16	22
Decerebration	8	32	26	35
Abnormal respirations	5	20	19	25
Hemiplegia	8	32	18	24
Unilateral fixed pupil dilatation	15	60	42	56
Bilateral fixed pupil dilatation	3	12	10	13
External signs of head injury	24	96	68	90
Other major injuries	3	12	10	13
Shock	0	0	9	12

depending upon pressure measurements by an intracranial catheter or upon the patient's neurological condition; (3) with controlled ventilation —we prevent hypercarbia, believing that an arterial carbon dioxide pressure between 30 and 35 mm of mercury is optimal and (4) with hypothermia—it is essential to prevent hyperthermia (body temperatures above 38°C) since both the cerebral metabolic demands and intracranial pressure rise as the temperature rises. Many neurosurgeons, including ourselves, try to reduce the patient's body temperature (to 33 to 35°C).

DR. BLAISDELL: *Would you comment on surgical decompression?*

DR. HOFF: We know that burr holes alone do not effectively reduce intracranial pressure. Large craniotomies, on the other hand, do reduce it. We also know that craniotomy is a more effective treatment for acute intracranial hematomas than is simple trephination, with a substantially different mortality rate between the two operations. Consequently we employ craniotomies for masses resulting from acute trauma, and use medical decompression when a mass cannot be identified.

It is obvious to all of us that current methods of surgical and medical management of severe head injury have not solved the many problems we confront in the patient with a traumatized brain. Renewed interest in head injury research may provide us with some of the answers we clearly need.

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Refer to: Barbour BH, Lambert MC, Fisher SR: Medical audit in action—Experience in a regional kidney disease program. West J Med 121:439-442, Nov 1974

Progress in
PUBLIC ACCOUNTABILITY

Medical Audit in Action

Experience in a Regional Kidney Disease Program

BENJAMIN H. BARBOUR, MD, *Los Angeles* • MARK C. LAMBERT, MD, *San Francisco*
STANLEY R. FISHER, MD, *Irvine*

The California Medical Association (CMA) has developed an educational patient care audit workshop to meet a growing voluntary interest among practicing physicians in California in methods for improving the quality of care. Through programs in continuing education, the workshop demonstrates steps in objective assessment of current quality and potential areas in need of improvement, as well as ongoing results from attempts to improve medical practice. Added to this original voluntary physician participation is increasing interest in quality assurance among community hospitals, health professional schools and all types of health-oriented personnel stimulated by recent passage in California of PL 92-603.

Public Law 92-603 establishes the requirement that Professional Standards Review Organizations (PSRO's) be formed to review the necessity and quality of health services provided under Medicare and Medicaid (Medi-Cal). Further, the law states that where such review is satisfactorily performed locally (for instance, within a health care setting) and independently (that is, by the health care practitioners themselves), review by the PSRO will be obviated. The increasing demand for public accountability in all spheres has probably accounted for this aspect of the legislation.

The management of chronic renal disease by hemodialysis and/or transplantation is now a service which is covered by Medicare. The legislation specifically authorized the Secretary of HEW to establish minimal utilization rates in facilities and medical review boards to screen the appropriateness of patients for the proposed treatment modality. Each of these functions is of the same nature that PSRO's are charged to review. The CMA workshop approach, as an alternative to PSRO review, would allow practitioners a method which, in addition to assessing quality of care offered their patients, saves the physician time and provides a means for improvement in patient care.

The renal program at Los Angeles County-University of Southern California (LAC-USC) Medical Center was originally introduced to the CMA concept by coordination activities of Regional Medical Programs in California through their quality of patient care studies and the Regional Kidney Disease Program. It was felt that review boards, which may well be established to monitor the quality of patient care for dialysis and transplant patients, must have a basis for evaluating patient care and, therefore, must adopt a standard process which will lead to cooperative attitudes necessary for a health team in developing criteria for medical conditions.

If institutions and physicians involved in dialysis and transplantation who, in fact, involve a health team in this process, aggressively pursue the voluntary development of criteria, then organized medicine, governmental programs and, most importantly, the patient will have benefited. This paper will attempt to display the processes learned

Submitted May 14, 1974.
Reprint requests to: B. H. Barbour, MD, Department of Medicine (Renal Section), USC School of Medicine, Los Angeles County-USC Medical Center, 1200 North State Street, Los Angeles, CA 90033.

during the workshop as it relates to a specific medical-surgical team. The process developed by CMA is primarily directed toward a hospital team; however, similarities with respect to a major hospital service obviously exist. This paper also discusses the feasibility of implementing the patient care assessment process at the LAC-USC Medical Center, involving a health team consisting of physicians, nurses, social workers, technicians, food service workers, medical records administrators, hospital administrators and patients.

Workshop Program and Organization

The California Medical Association-Medical Audit Workshop was planned for a three-day period. The health care team which participated in the workshop included three physicians, three registered nurses, a dietitian, two medical social workers, a medical records administrator, an administrative assistant and two patients. The initial part of the program was directed toward defining the overall goals for a patient care audit committee. The necessity for the major goal to be directed toward excellent patient care was emphasized, and that criterion for patient care must be accepted by every physician whose medical records will be reviewed.

The medical audit process involves reviewing medical records which are derived from a specific diagnosis or problem. Criteria for the diagnosis or problem are defined and expected performance levels are established. The expected performance levels are thresholds for action if, upon review of medical records, actual performance levels do not meet or exceed them. Differences are analyzed and specific remedial action designed.

In principle, the facility or program within a facility will establish an efficient care audit committee and, in the case of the renal program, this committee was taken to consist of the representatives attending the workshop. Once the committee is established, the first step to be taken is to develop a draft of criteria with minimal acceptable performance levels. A second step is to have the drafted criteria ratified by all those whose cases may be audited. The third step would be to search the medical records for evidence that the criteria were fulfilled. This search is carried out by medical records personnel, that is, non-physicians. The fourth step involves the identification of criteria which failed to meet expected levels. An analysis (steps five and six) of the differences will suggest the remedial action to be taken and might involve an alteration of the original criterion (for instance, to increase specificity), educational programs, administrative changes or perhaps the acquisition of additional personnel or equipment (steps seven and eight). After some appropriate period of time, subsequent records should be reviewed against the original (or modified) criteria to determine if the remedial action was effective in correction of the problem. This completes the cycle and provides evaluation of the audit as a whole. This process is delineated in the accompanying list of steps and is similar to the concept developed by Brown and Uhl.[1]

STEPS IN THE AUDIT CYCLE

1. Select topic: diagnosis, operation or other basis for defining patient care audit. Specify objective.
2. Develop draft criteria and expected performance levels for each.
3. Have draft criteria (or revisions) and performance level ratified by all those whose cases may be audited.
4. Apply criteria to chart review by medical records personnel.
5. Identify areas where actual performance does not equal expected performance.
6. Analyze problems and determine probable causes.
7. Develop specific remedial action.
8. Implement remedial action.
9. Reaudit topic after suitable interval to monitor effectiveness of remedial action, evaluate the specific audit and the process as a whole.

The workshop began by the development of criteria. The diagnosis for which criteria were developed were renal homotransplantation and chronic renal failure. The criteria for transplant diagnosis and expected performance levels were established (Table 1). Also established were criteria and performance levels for chronic renal failure (Table 2). Each criterion was established only after ascertaining its relevance, its understandability, its measurability, its effect on behavior and its achievability.

It was decided by the patient care audit committee that, upon chart review, evidence of the criteria being met should be as indicated in the Tables. For example, in the cases where diagnosis was chronic renal failure, the level of performance for a notation about attempts being made to obtain an x-ray study of the kidneys or an indication of kidney size or a kidney biopsy should be 90 percent.

The system was tested by review of ten randomly selected medical records with each of the two diagnoses. The results indicated that there

TABLE 1.—*Transplant Diagnosis*

Criteria	*Expected Performance Levels (Percent)*	*Actual Performance Levels (Percent)*
1. Complete preoperative checklist should be in chart	100	100
2. All white counts should be greater than 3,500 and platelet count greater than 50,000	90	50
3. There should be no temperature elevation greater than 100°F, without blood and urine culture and chest x-ray	100	60
4. There should be no diastolic blood pressure greater than 110 on two successive days	90	80
5. There should be no weight change greater than four pounds postoperatively on any given day after the first day	95	80
6. There should be no infection after operation	80	80
7. No more than two units of blood should be given in the postoperative or operative period, and only frozen blood should be administered	100	40
8. Each patient should have social service, dietary, and nursing notes indicating that each of these disciplines rendered counsel to the patient	100	10

TABLE 2.—*Chronic Renal Failure Diagnosis*

Criteria	*Expected Performance Levels (Percent)*	*Actual Performance Levels (Percent)*
1. A notation about attempts being made to obtain an x-ray of the kidneys, or a kidney x-ray report, or a notation about kidney size, or a kidney biopsy should be in the record	90	80
2. A chest x-ray should be in the record	95	90
3. The following blood tests should be in the record: creatinine, BUN, sodium, potassium, bicarbonate, calcium, phosphorus, alkaline phosphatase, uric acid and hematocrit		
4. A cardiac and neurologic examination should be recorded	95	90
5. A serum bicarbonate less than 15 on two successive days should not occur	90	100
6. A serum potassium over 6 more than one day should not occur	95	100
7. Social service and dietetic counseling should be indicated in the medical record	80	100
8. The administration of any one of the following drugs should not occur: spironolactone, triamterine, potassium chloride, ammonium chloride and methenamine	90	80

were problems within several of the criteria set for each diagnosis. For example, criterion 3, Table 1, indicated that there should be no body temperature elevation greater than 100°F without blood and urine cultures and a chest x-ray film. However, this criterion was met by chart review in only 60 percent of the cases. The patient care audit committee reviewed the findings and recommended the findings should be publicized to the physician house staff and nursing house staff who are responsible for caring for these patients.

The worst performance was for criterion 8, Table 1. It was discovered by the patient care audit committee that the social service and dietary disciplines had not recorded the fact that they had rendered a patient service. Consequently, it was recommended that personnel in each of these disciplines make a notation in the medical record when patient counseling is given. Through perusal of the Tables, it is apparent that several criteria which were agreed upon by the medical care team were not being fully met. This discovery was accepted as an important piece of information for the medical care team and enthusiasm was generated toward improving the performance level. The number of medical records reviewed during the workshop was small, only 10 records for each diagnosis. Consequently, the results do not accurately reflect the overall performance of the criteria established by the Renal Section of the LAC-USC Medical Center and can only be used for illustrative purposes.

Comment

A primary goal of the California Medical Association's Patient Care Assessment (or Medical Audit) Workshop Program is to encourage health care teams objectively to examine the quality of health care they provide as compared with their own standard of quality. In contrast to quality assessment by means of random chart review, this method is designed to reflect not upon isolated and

individual variations or deviations (deficiencies) in patient care, but rather upon trends observed in numerous records of patient care (performance levels). Specific variations in single individual records, if deemed of such significance that a special review by a physician is called for, may be indicated by this process as well.

In many instances, mere recognition of sub-optimal performance by the health practitioners will be corrective; that simple recognition may not solve the problem, however, has been pointed out previously[2] in a study which demonstrated that habit pattern could be modified only through repetitive stimulation. The California Medical Association's Medical Audit Program allows for the development of unique methods to stimulate performance through the work of the patient care audit committee. The audit committee may decide that once performance is falling below the minimal acceptable level an alert system is necessary in order to improve the performance level.

A major advantage of this program is working within the existing system of health care delivery. In the workshop described herein, health professionals and patients made up the audit team on an experimental basis.

The inclusion of patients in the patient care audit committee was particularly stimulating to the committee members, who established criteria for the recognition of good medical care. The patients were able to point out how the criteria became relevant to their feelings over important issues. For example, patients emphasize their concern over clear dietary instructions. Additionally, they pointed out the importance of economic and social factors in their ability to adhere to medical regimens. Both dietary and social counseling were finally considered important criteria for good medical care to the patient with chronic renal disease. Patients who work on a patient care audit committee would more likely be those who are articulate, intelligent and emotionally stable.

Emotional stability is perhaps of the greatest importance because, during the discussions of criteria by the audit committee, elements of uncertainty about "best" criterion are bound to arise. A temperamental patient could become anxious and lose confidence in the health care team. This reaction did not occur in the patients included in the renal program patient care audit committee. These patients were well known to the health care team and had been under the care of the renal program at LAC-USC Medical Center for several years. They were known to be physically and mentally stable at the time they were asked to serve on the patient care audit committee.

In the final analysis, medical care is a service to patients; therefore in the appraisal of its effectiveness, patients (the consumer) would appropriately be involved in making this appraisal. Much of medical care is delivered in an authoritarian manner, perhaps an inevitable result when highly specialized knowledge is applied to a problem, but it is certainly reasonable to include the consumer in judging the final product even in the most specialized fields. Acceptance of medical care will reach the highest level when the patient understands the process and criteria of medical care.

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Special Article

Refer to: Hurwitz S: Medical aspects of adolescents participating in sports. West J Med 121:443-447, Nov 1974

Medical Aspects of Adolescents Participating in Sports

SAMUEL HURWITZ, MD, *San Francisco*

As a result of an increase in various hormone levels in adolescence, there occurs a rapid and extensive growth in height, weight, muscle mass and sexual maturity. These changes bring new and greater nutritional requirements. The need for protein, iron, calcium and calories is particularly high. Normal adolescents differ greatly in the timing, rate and extent of their growth. Therefore, chronological age is a deceptive yardstick in planning a physical program for adolescents.

Other features of this age period are identity problems, acting out and impulsive behavior. In some instances goals which seem unattainable are denied by the adolescent (for instance, a boy may say that he doesn't want to be on the team). He may become self-scorning and self-belittling because of unrealistically high aspirations for himself. Fearing criticism or ridicule, he becomes uncommunicative. He may seek to dispel uncertainties regarding courage by acts involving physical hazard. Anger and despair may even lead to suicide (the third most common cause of death in adolescence). Many adolescents are not ready for the intense emotional stress of competition, but all require continued reassurance and genuine interest.

The basic objective should be the same in all physical education programs: to provide the most pleasant physical activity that will help the student attain maximum "fitness" (defined as the ability to function at one's best level of efficiency in all daily living). Thus physical exercise, in addition to providing an approved outlet for an adolescent's excess energy, may be of great therapeutic value in some social and emotional problems of adolescence.

Some conditions seen in adolescents are also seen in adults, but there also are some that are unique or occur more commonly in adolescence. Furthermore a delayed sequence and extent of bone and muscle development, and weakness inherent in the epiphyseal plate, may lead to more severe complications in adolescents subject to athletic injury. Some of the conditions observed in the teenager are (a) osteochondritis (for instance, Osgood-Schlatter disease) and epiphysitis (juvenile vertebral epiphysitis which may result in kyphosis, "little leaguer's elbow"), (b) slipped femoral epiphyses, (c) osteochondritis ossificans, (d) spondylosis (weak back), (e) "duck neck" (marked weakness of the cervical strap muscles, a condition in which the patient is constantly sustaining cervical sprains), (f) subluxing patella, (g) quadriceps insufficiency, (h) recurrent dislocation, (i) avulsion, (j) tenosynovitis and, a very serious condition, (k) premature epiphyseal closure with resulting undergrowth of the part.

For the health and welfare of the athletes, certain features should be considered essential to a sports program: (1) proper medical supervision and care; (2) adequate conditioning; (3) proper instruction of skills; (4) properly fitted, well-constructed and well-designed equipment; (5)

From the Department of Public Health, City and County of San Francisco, Francis J. Curry, MD, Director.

Reprint requests to: S. Hurwitz, MD, Northeast Health Center, 1490 Mason Street, San Francisco, CA 94133.

proper facilities for competition; (6) application of sound health principles in the care of equipment, as well as of locker rooms, showers and other facilities; (7) competent use of a well-regulated rules code and (8) first aid instruction for prevention and treatment of injuries and for rehabilitation of injured athletes.

Proper Medical Supervision and Care

Ideally an adolescent athlete should have at least one physical examination each year. With any intervening illness, injury or operation, a medical clearance should be required before return to full activity. The physical examination should be done under conditions that enable the physician (a) to determine the health status of the participant, (b) provide medical advice regarding optimum health fitness, (c) restrict the activities of those whose physical limitations present undue risk and assign them to selected programs and (d) suggest means of curtailing injury and improving safety. The student's own private physician is best equipped to do this, and mass examinations are totally unsatisfactory and should not be condoned. The medical workup should include evaluation of past illnesses, injuries and operations. The immunization record is of importance so that the physician will know for what, and when, the individual has received injections. An initial course of three tetanus injections (usually given with diphtheria and whooping cough) in the first year of life, with a booster in the second year and again before entering primary school, will provide protection for at least ten years thereafter. Any severe lacerating injury a year after injection might merit a booster inoculation. Polio immunization should be considered essential since the role of trauma in localizing paralysis has often been cited. In addition, a lasting protection against rubeola, rubella and mumps is available with only one injection of a combined vaccine and will certainly aid in decreasing the absentee incidence for illness in any program. A blood test, urine examination, tuberculin test and, if possible, a chest x-ray study are worthwhile for a complete evaluation. Physiologic exercise testing is of help in evaluating cardiovascular functional capacity, particularly as a means of clearing adolescents for strenuous exercise programs, and to evaluate responses to conditioning programs. Where special apparatus is not available, objective methods (such as noting the heart rate and observing transient fatigue, breathlessness, weakness or other symptoms) will be useful in regulating training programs.

It is helpful to divide sports into several categories. Baseball, football, basketball, soccer, hockey, lacrosse and wrestling may be classed as contact sports. Non-contact sports may be divided into those requiring endurance (swimming, track and cross-country running, tennis and rowing) and others (such as bowling, archery and golf). This will enable a more intelligent evaluation of conditions for disqualifying participation in any particular sport.

I shall list the medical conditions which should disqualify an athlete from participating in contact sports.

- *Neurologic conditions:* (1) large cranial defects following intracranial surgery (2) inadequacy of the neuromuscular system, congenital or acquired, that is incompatible with the contact or skill the sport demands and (3) a history of three concussions. As regards epilepsy, a statement issued several years ago by the Committee on Sports Medicine of the American Medical Association stated that epileptics should not participate in contact sports. Recently Livingston, of Johns Hopkins Medical School, stated that he has not seen, in over 15,000 cases, any convulsions precipitated by head trauma in epileptics whose seizures were under control (free of seizures for at least one year). Psychologically more harm may be done by restricting participation instead of allowing such an individual to lead as normal and active a life as possible.
- *Eye conditions:* (1) absence of one eye or severe amblyopia of one eye (20/200 corrected), (2) retinal detachment (repaired or unrepaired) and (3) congenital glaucoma.
- *Ear conditions:* deafness or pronounced impairment of hearing which might endanger the individual's welfare.
- *Cardiovascular conditions:* (1) active rheumatic fever and 1 year after carditis has subsided, (2) cardiac enlargement, (3) severe valvular lesions (mitral stenosis, aortic stenosis), (4) previous heart surgery for congenital or acquired disease and (5) hypertension on any organic basis.
- *Pulmonary conditions:* (1) active tuberculosis (not just on isonicotinic acid hydrazide) and (2) emphysema. Asthma per se is not a contraindication but there should be a ready access to medication when necessary.
- *Abdominal conditions:* (1) any enlarged major abdominal organ (spleen, liver, kidney),

(2) absence or pronounced impairment of one of paired organs (kidney, testis and so forth), (3) active kidney infection and (4) inguinal hernia (which should be immediately repaired).

- *Metabolic conditions:* (1) uncontrolled diabetes, (2) hyperthyroidism, (3) hyperparathyroidism and (4) Cushing's syndrome.
- *Hematologic conditions:* (1) bleeding tendency and (2) coagulation defects.
- *Osseous conditions:* (1) active osteochondritis (Osgood-Schlatter disease, which is disabling), (2) slipped femoral epiphyses, (3) chronic osteomyelitis, (4) recurrent dislocation of the shoulder and (5) metabolic bone disease resulting in skeletal weakness. With regard to amputees, if the integrity of the affected limb is medically affirmed and the nature of the sport does not impose undue risk for the amputee, teammates or opponents, participation in contact sports may be allowed.

Conditioning

A year-round program of physical conditioning is advocated for all adolescents, especially those interested in athletics. Each coach will utilize those methods and means to accomplish ends which he considers most desirable, and will construct a program of training and conditioning that will best meet the physical and psychological needs of his squad. There should be a minimum of three to four weeks of practice before the first official game. Practice periods of reasonable duration (about 1½ hour limit) are desirable. Any program should be aimed at maintaining optimum weight level, increasing strength, endurance, flexibility, skill, speed of movement, acclimation, psychological readiness, and the practice of desirable health habits. Self-discipline should be instilled early in the athlete. The adolescent should be encouraged to get eight hours sleep; consume a proper, nutritious diet and avoid smoking, alcoholic beverages and all possible drugs. The use of dietary supplements (such as vitamins, wheat germ and aminoacids) has shown no demonstrable effect in increasing efficiency and is costly and unnecessary. Contrary to the view that a steak meal should be consumed before a game, it would seem to make more sense physiologically to increase the glycogen content of the body, which supplies the energy for the athlete's effort, by a high carbohydrate diet for 24 to 36 hours before strenuous activity.

A resolution adopted by the 1972 House of Delegates of the American Medical Association calls upon all physicians to exert rigid control over the prescribing of stimulant and sedative drugs, and androgenic anabolic steroids, to athletes. Habituation to amphetamines can lead to problems of insomnia, headache, acute anxiety state and circulatory collapse—without improving performance level. Medication of normal athletes with androgenic substances is without benefit and may cause a disturbance of metabolic processes (such as retention of salt and water, interruption of growth and psychic changes—particularly dangerous in adolescents who have not yet formed and stabilized their personalities as young adults) and, possibly, prostatic cancer.

Aching muscles, joints, and tendons are common in the early stages of exercise and are normally the result of inappropriate conditioning at too rapid a pace. Most musculoskeletal complaints respond rapidly to a reduced pace or temporary discontinuance of the program. Headaches during football practice are not uncommon, and only very rarely indicate neurological or vascular illness which may be aggravated by playing. Frequently such headaches are overcome by attention to proper fitting of the helmet, overall conditioning with particular attention to strengthening the neck muscles, prevention of mild forms of heat exhaustion and correction of defective vision or dental problems. These headaches usually disappear as the athlete gets into better shape. Obese youngsters should be advised about sensible weight reduction and should not attempt too much exercise at the start of a conditioning program. Rapid weight loss by drastic diet or dehydration measures can be harmful and cause cardiovascular difficulties. In unusual environmental conditions (excessive heat and humidity), in times of stress or emotional turmoil or following ingestion of a heavy meal, exercise should be decreased or temporarily abandoned. Furthermore, under climatic conditions of high temperature and humidity, the drinking of water freely during the workout should be encouraged. Ordinarily the extra salting of food will usually be sufficient to prevent serious electrolyte imbalance, but a salt solution (¼ tsp to 1 qt of water) or a commercial product such as Gatorade® can be used. A warm-up period of three to five minutes before active participation in a game and, possibly, a tapering off period after strenuous activity should be recommended. Excessively hot showers are to be avoided immediately after exercise as in rare instances they have

been associated with manifestations of myocardial infarction. Incidentally, it is well to emphasize that after recovery from heat stroke there are no long term ill effects and recurrence is not made more likely.

Proper Teaching of Skills

This subject, of course, falls within the domain of the coach but medical advice is often sought. It should again be pointed out that motor skills, agility, coordination and strength are variable and should be carefully considered in placing an adolescent in the type of sport best suited to him. It should be emphasized that with adolescents chronological age is a poor criterion for evaluating and planning. Of much more value is their state of growth and development (epiphyseal age [judged, for instance, from x-ray films of the wrist and hand]) and secondary sexual characteristics (maturation rating). A good coach can command respect and admiration from hero-worshipping teenagers and serve as an inspiration to them. On the other hand, I am reminded of the story of the football coach who, while giving a pre-game pep talk to his team, said "remember that football develops individuality, initiative and leadership. Now get in there and do exactly as I tell you."

Properly-Fitted, Well-Constructed and Adequately Maintained Equipment

Good equipment is essential if injuries are to be minimized. It has been shown by Robey of North Carolina that football players with suspension type football helmets have a lower injury rate than those with padded helmets. It also was shown that the Rawings CP, UP_2 and HPO shoulder pads were superior to all other types and makes in prevention of injury to the shoulder girdle area. From a three year statewide study by the New York Public High School Athletic Association, it was concluded that two equipment combinations—a low shoe, disc heel, ankle wrap and low shoe, short cleats, no ankle support—produced a statistically significant lower rate of serious injuries of the lower extremities, particularly of the knee. It was recommended that varsity high school football players be outfitted with low shoes and some form of disc or flat heel or short cleats and that the sole cleats on football shoes be shortened as soon as possible. Helmets for soccer goalies (to prevent head injuries when on the ground); better helmets for baseball players; protective headgear, shatterproof glasses and properly fitting mouth pieces for hockey players have all helped reduce the incidence of athletic injuries. This reduction can best be accomplished by giving sufficient attention to their prevention. Thus the search for better equipment (for instance, modification in collar design to offer better protection against football flexion injuries) continues constantly as one means to this end.

Proper Facilities for Competition

Adequate sports facilities are a vital part of any program which seeks to minimize morbidity in sports. The type of turf and its proper maintenance for football, adequate space for basketball courts, elimination of unnecessary hazards alongside fields and courts, proper locker room facilities and showers are all factors that can reduce the extent of injury and illness.

The Application of Sound Health Principles

The importance of sound principles in the care of equipment, locker rooms, showers and the like is quite obvious. Thorough cleanliness, frequent washing of playing apparel and proper attention to foot gear will help prevent many of the small debilitating conditions such as blisters, fungus and other skin diseases.

Competent Officiating Under the Rules Code

It has been estimated that approximately 10 percent of all football game injuries in high school occur as a result of violations of the rules. Thus constant attention should be paid to upgrading the understanding and skills of all officials who have a major responsibility for the safety of play. Furthermore, rule codes can be and are being constantly improved for the safety and protection of the participants. A survey of New York state high schools has shown that changes can be initiated that result in greatly diminished morbidity (for instance, eliminating spearing and revising blocking rules to exclude check-back and blind side blocking).

First Aid Instruction for the Prevention and Treatment of Injuries

Instruction in first aid should be an integral part of any sports program. Every contact sport needs a physician sitting on the bench or, at least, readily available. Every trainer and coach should be familiar with the most common types of injuries (which in adolescents are sprains, muscle contusions, strains and joint contusions). Different sports

are most commonly associated with particular injuries. Football is associated with sprains and contusions, concussions, neck injuries, knee and lower extremity injuries, contused viscera, shoulder dislocations and fractures. Basketball is associated with strains and sprains; internal derangement of knee joints and fractures of wrists, feet and ankles. In baseball, hand, elbow and shoulder problems (epiphysitis and osteochondritis) are seen, as well as fractures of the lower extremities. Soccer is associated with comminuted tibial fractures and track with fatigue and avulsion fractures.

There is no proper place in sports for the use of local anesthetics to eliminate pain so that a player can continue in the game. If they are used, an injury may be made worse and the injured athlete's future athletic activity endangered. The local injection of steroids into acutely injured soft parts may result in delayed healing of the tissues by virtue of the catabolic effects of the drug. There is also very little objective evidence from controlled studies that the injection of hyaluronidase, an enzyme that has been used in the treatment of selected athletic injuries for several decades, is of any value in speeding wound healing and repair. Prolonged breathing of oxygen before exercise, as is sometimes done, is ineffectual as it is impossible for the body to store it, and there is no evidence that breathing oxygen hastens recovery from fatigue or improves performance.

After a concussion a player should be removed and kept out of further participation in that game. Recovery from a mild concussion occurs within a few days but it would be well to recommend gradual resumption of activity and not allow full activity for about a week. With a more severe concussion, an athlete should not be allowed to play until all signs and symptoms have cleared. Two concussions should keep an athlete out for the season and three should remove him from contact sports. After a shoulder dislocation, an athlete should not return to play before six weeks—and then with a proper protective device.

When the diagnosis of injury to an important organ or structure is in doubt, an adolescent should not be permitted to resume competition until all the signs and symptoms have cleared. Whenever there is the possibility that participation may aggravate even a minor injury, an athlete should temporarily be removed from competition. The physical standards for return to competition are (1) restoration of muscles to full strength when weakness has resulted from the injury, (2) recovery of function of a major joint as shown by a full range of painless motion and no instability and (3) clinical and x-ray evidence of solid union in a factured bone. For the final decision, the athlete should be observed by physician and coach or trainer for his agility and facility of performance. An adolescent often is impatient to return to activity but his future welfare must not be jeopardized in an attempt to ensure victory. An inefficiently treated injury may result in a subsequent deprivation of those opportunities to gain acceptance and self-confidence which athletics offer.

The positive values of sports should be emphasized because of their social, psychological and emotional values. All possible safeguards should be taken to protect the health and welfare of participants. Adequate evaluation, supervision of playing areas to make them free of hazards, proper conditioning, good coaching, the best possible equipment and its judicious care, and adequate treatment and proper rehabilitation, will serve to reduce and minimize athletic injuries.

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in memoriam

Back, James B., Upland. Died September 20, 1974 in Upland of cancer of the stomach, aged 35. Graduate of Vanderbilt University School of Medicine, Nashville, 1965. Licensed in California in 1971. Dr. Back was a member of the San Bernardino County Medical Society.

Barden, Robert Bradshaw, Lake Arrowhead. Died September 8, 1974 in Lake Arrowhead, aged 64. Graduate of the University of Southern California School of Medicine, Los Angeles, 1955. Licensed in California in 1956. Dr. Barden was a member of the San Bernardino County Medical Society.

Barksdale, Robert W., Hayward. Died September 5, 1974 of heart disease, aged 64. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1946. Licensed in California in 1946. M.D. degree from California College of Medicine, 1962. Dr. Barksdale was a member of the Forty First Medical Society.

Falk, Harry L., El Monte. Died September 19, 1974 of cerebrovascular accident, aged 67. Graduate of the University of Minnesota Medical School, Minneapolis, 1937. Licensed in California in 1938. Dr. Falk was a member of the Los Angeles County Medical Association.

Harris, William L., Los Angeles. Died August 18, 1974 in Los Angeles of cardiac arrest due to subarachnoid hemorrhage, aged 49. Graduate of Howard University College of Medicine, Washington, DC, 1955. Licensed in California in 1961. Dr. Harris was a member of the Los Angeles County Medical Association.

Harwick, Herbert J., Los Angeles. Died July 31, 1974 in Los Angeles of astrocytoma of the brain, aged 33. Graduate of University of California at Los Angeles, School of Medicine, 1964. Licensed in California in 1965. Dr. Harwick was an associate member of the Los Angeles County Medical Association.

Herring, Elmer Franklin, Sherman Oaks. Died September 4, 1974 in Sherman Oaks of cerebral hemorrhage, aged 74. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1931. Licensed in California in 1955. Dr. Herring was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Jacobs, Albert M., San Francisco. Died March 25, 1974 on the high seas near Sydney, Australia of heart disease, aged 82. Graduate of Northwestern University Medical School, Chicago, 1921. Licensed in California in 1921. Dr. Jacobs was a member of the San Francisco Medical Society.

Kennedy, Dean M., jr., Los Angeles. Died August 4, 1974 in Los Angeles of gastrointestinal hemorrhage and bone marrow aplasia, aged 55. Graduate of the University of Southern California School of Medicine, Los Angeles, 1946. Dr. Kennedy was a member of the Los Angeles County Medical Association.

Kobayashi, Norman T., Gardena. Died September 4, 1974 of myocardial infarction and cancer, aged 67. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr. Kobayashi was a member of the Los Angeles County Medical Association.

Leland, Harold Galen, El Cajon. Died September 16, 1974 in La Mesa, aged 78. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1923. Licensed in California in 1923. Dr. Leland was a member of the San Diego County Medical Society.

Lindsey, Ralph Everett, Redondo Beach. Died July 23, 1974 of cancer of the spine, aged 75. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1948. Licensed in California in 1949. M.D. degree from California College of Medicine, 1962. Dr. Lindsey was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Murray, Dwight H., sr., Napa. Died October 7, 1974 in Napa of cancer, aged 86. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1917. Licensed in California in 1920. Dr. Murray was a past president of the American Medical Association, a past honorary president of the California Medical Association, and a past president of the Napa County Medical Society, a retired member of the Napa County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Stafford, Clarence E., Los Angeles. Died August 4, 1974 in Glendale of myocardial infarction, aged 67. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Dr. Stafford was a member of the Los Angeles County Medical Association.

Wachtel, Michael, Alameda. Died September 17, 1974 in Alameda of pulmonary emphysema, aged 72. Graduate of Ludwig-Maximilians-Universität, Medizinische Fakultät, München, 1927. Licensed in California in 1939. Dr. Wachtel was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Werthmann, Paul Anthony, San Jose. Died September 21, 1974 in San Jose of cancer, aged 72. Graduate of Loyola University School of Medicine, Chicago, 1932. Licensed in California in 1932. Dr. Werthmann was a member of the Santa Clara County Medical Society.

Wright, John Madden, Pasadena. Died September 7, 1974 in Pasadena of pneumonia, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1929. Dr. Wright was a member of the Los Angeles County Medical Association.

The new nutritional margarine labels have a message about you.

INFORMATION ON FAT AND CHOLESTEROL CONTENT
IS PROVIDED FOR INDIVIDUALS WHO,
ON THE ADVICE OF A PHYSICIAN,
ARE MODIFYING THEIR TOTAL DIETARY INTAKE
OF FAT AND CHOLESTEROL.

Mandatory nutritional statement on the back of all margarine labels

Saffola® wants you to get the rest of the message.

MAZOLA

Nutrition Information Per Serving

erving size	14 grams (about one tablespoon)
ervings per container	32
alories	100
rotein	0 grams
arbohydrate	0 grams
at	11 grams
Percent of calories from fat	99%
Polyunsaturated	3 grams
Saturated	2 grams
Cholesterol	0 (0. per 100 grams)
odium	120 milligrams (865 mg./100 gm.)

ercentage of U.S. recommended daily allowances (U.S. RDA)

itamin A 10%

ontains less than 2 percent of the U.S. RDA of pro-in, Vitamin C, thiamine, riboflavin, niacin, Calcium, nd iron.

nformation on fat and cholesterol content is provided r individuals who, on the advice of a physician, are odifying their total dietary intake of fat and cholesterol.

IMPERIAL

Nutrition Information Per Serving

Serving size	14 grams (about one tablespoon)
Servings per container	32 (per pound container)
Calories	100
Protein	0 (not a significant source of protein)
Carbohydrate	0
Fat	11 grams
Percent of calories from fat	over 99%
**Polyunsaturated	3 grams
**Saturated	2 grams
**Cholesterol	0 (0. per 100 grams)

*Percentage of U.S. recommended daily allowances (U.S. RDA)**

Vitamin A 10% Vitamin D 15%

*Contains less than 2 percent of the U.S. RDA of Vitamin C, thiamine, riboflavin, niacin, calcium, and iron.

**Information of fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

SAFFOLA

Nutrition Information Per Serving

Serving size	14 grams (about one tablespoon)
Servings per container	32 (per pound container)
Calories	100
Protein	0
Carbohydrate	0
Fat	11 grams
Percent of calories from fats	100%
Polyunsaturated	5 grams
Saturated	2 grams
Contains no cholesterol	

Information of fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

Percentage of U.S. recommended daily allowances (U.S. RDA)

Vitamin A 10% Vitamin E 15%

Contains less than 2 percent of the U.S. RDA of protein, Vitamin C, thiamine, riboflavin, niacin, calcium, and iron.

With the new nutritional labeling, it's all there in black and white. So you can see for yourself. And so can your patients. It adds up to this: Saffola is higher in polyunsaturates than most other margarines including corn oil. And no other margarine is lower in saturated fats than Saffola. Of course, all our products, including Saffola oil and mayonnaise are made with safflower oil.

But we're not kidding ourselves. We know that even if you advise a fat modified diet, your patients might not switch to Saffola. Not unless it tastes every bit as good or better than the spread, oil or mayonnaise they're now using. That's something else they're going to find out for themselves.

The Role of the Detail Man

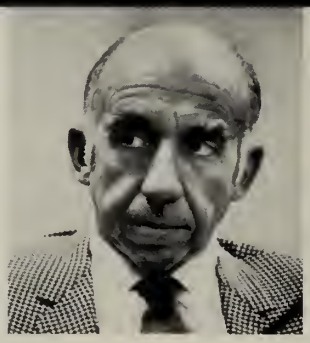
Opinion & Dialogue

Dr. Willard Gobbell
Family Physician
Encino, California

"I may be prejudiced, but I a very much in favor of the detail m I meet. Most of them are knowled able about the drugs they promot and can be a great help in acquair ing me with new medication."

Family Physician's Perception

I think that most general practitioners in this area feel as I do about the detail man. Over the years I have gotten to know most the men who visit me regularly an they in turn have become aware o my particular interests and the na ture of my practice. They, therefore, limit their discussion as muc as possible to the areas of interes to me. Since I usually see the sam representative again in future visits, it is in his best interest to supply me with the most honest, factual, as well as up-to-date information about his products.



Dr. Jeremiah Stamler
Chairman
Department of Community Health and Preventive Medicine, and Dingman Professor of Cardiology
Northwestern University Medical School

"In the total picture of deali with health problems in this cour there is a potential for detail men to play a meaningful role."

The Positive Influence

My contact with representa tives and salesmen of the pharma ceutical industry is the type of co tact that people in a medical cent research people, and academic people have and that's in all likeli on a somewhat different level fro that of the practicing physician.

Let me touch on how I perso ally perceive the role of the sales representative. These men reach large numbers of health professionals. Thus they could be—anc at times actually are—dissemina tors of useful information. They could consistently serve a real ed cational function in their ability t discuss their products.

At present they do distribut printed material, brochures and pamphlets—some of it scientific ally sound and therefore truly use ful—as well as some excellent fi produced by the pharmaceutical industry. When they function in t

a Source of Information?

Yes, with certain reservations. verage sales representative great fund of information the drug products he is re- ible for. He is usually able to r most questions fully and gently. He can also supply ts of articles that contain a deal of information. Here, xercise some caution. I usu- cept most of the statements inions that I find in the s and studies which come he larger teaching facilities. s without saying that a physi- hould also rely on other es for his information on acology.

ng of Sales Representatives

deally, a candidate for the on as a sales representative armaceutical company d be a graduate pharmacist as a questioning mind. I don't his is possible in every case, it becomes the responsibility of the pharmaceutical company to train these individuals comprehensively. It is of very great importance that the detail man's knowledge of the product he represents be constantly reviewed as well as updated. This phase of the sales representative's education should be a major responsibility of the medical department of the pharmaceutical company.

I am certain that most of these companies take special care to give their detail men a great deal of information about the products they produce—information about indications, contraindications, side effects and precautions. Yet, although most of the detail men are well informed, some, unfortunately, are not. It might be helpful if sales representatives were reassessed every few years to determine whether or not they are able to fulfill their important function. Incidentally, I feel the same way about periodic assessments of everyone in the health care field, whether they be general practitioners, surgeons or salesmen.

Value of Sampling

I personally am in favor of limited sampling. I do not use sampling in order to perform clinical testing of a drug. I feel that drug testing should rightly be left to the pharmacology researcher and to the large teaching institutions where such testing can be done in a controlled environment.

I do not use samples as a "starter dose" for my patients. I do, however, find samples of drugs to be of value in that they permit me to see what the particular medication looks like. I get to see the various forms of the particular medication at first hand, and if it is in a liquid form I take the time to taste it. In that way I am able to give my patients more complete information about the particular medications that I prescribe for them.

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ity they are indeed useful; ularly in the fact that they minate broadly based educa- material and serve not just shers" of their drugs.

her Side of the Coin

bviously, the pharmaceuti- npanies are not producing all aterial as a labor of love— e in the business of selling cts for profit. In this regard bitious and improperly moti- sales representative can negative influence on the cing physician, both by pre- g a one-sided picture of his ct, and by encouraging the ioner to depend too heavily gs for his total therapy. In ways, the salesman has often ed objective reality and mined his potential role as an or.

dustry Responsibility

ince the detail man must be rmation resource as well as sentative of his particular aceutical company, he be carefully selected and thoroughly trained. That training, perforce, must be an ongoing one. There must be a continuing battle within and with the pharmaceutical industry for high quality not only in the selection and training of its sales representatives, but also in the development of all of its promotional and educational material.

The industry must be ready to accept constructive as well as corrective criticism from experts in the field and consumer spokesmen, and be willing to accept independent peer review. The better educated and prepared the salesman is, the more medically accurate his materials, the better off the pharmaceutical industry, health professionals and the public—*i.e.*, the patients—will be.

Physician Responsibility

The practicing physician is in constant need of up-dated information on therapeutics, including drugs. He should and does make use of drug information and answers to specific questions supplied by the pharmaceutical representative. However, that information must not be his main source of continuing education. The practitioner must keep up with what is current by making use of scientific journals, refresher courses, and information received at scientific meetings.

The practicing physician not only has the right, but has the responsibility to demand that the pharmaceutical company and its representatives supply a high level of valid and useful information. I feel certain that if such a high level is demanded by the physician as well as the public, this demand will be met by an alert and concerned pharmaceutical industry.

From my experience, my impression is that sectors of the pharmaceutical industry are indeed ethical. I challenge the industry as a whole to live up to that word in its finest sense.

Pharmaceutical Manufacturers Association
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P·M·A

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

"...and she'd jump every time the phone rang."

"All right, I agree, she was obviously very anxious...you said she hadn't been sleeping..."

"She felt *tired enough* to sleep... not relaxed enough...food, too... she's too nervous to eat...says she *can't* relax...afraid there's something very wrong with her."

"...that's a good place t
Did you find anything w
with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

MSD MERCK SHARP & DOHME

For a brief summary of prescribing information, please turn to the following page.

hing... negative... nothing
cally wrong. Still has a
t of somatic complaints.
ed to reassure her... to let
k... to help her sort things
ne's been in to see me a
r of times."

"...what about medication?"

"Just what I was coming to...
I've had her on tranquilizers.
And *that's* what puzzles me. I'm
not getting the response I hoped
for. She's no better... perhaps a
little worse. It's sad to see."

"...I think *'sad'* may be what
you're not seeing! You know,
this sounds like another case
where the *anxiety* is so clear and
pervasive we tend to overlook
the depressive part of the picture.
I'm not sure that we shouldn't
almost always think of anxiety
with depression... not anxiety
alone. Take another look at your
records... talk to her some more.
If you decide she's depressed,
I think you might want to
consider TRIAVIL.... It can help
relieve her entire symptom
complex... control the anxiety...
while at the same time treat
the depression."

TRIAVIL®

to help treat what you often find: obvious moderate to severe anxiety with a less obvious underlying depression

containing perphenazine and amitriptyline HCl

a tranquilizer-antidepressant

Available:
TRIAVIL® 2-25: Each tablet contains
2 mg perphenazine and 25 mg amitriptyline HCl

TRIAVIL® 2-10: Each tablet contains
2 mg perphenazine and 10 mg amitriptyline HCl

TRIAVIL® 4-25: Each tablet contains
4 mg perphenazine and 25 mg amitriptyline HCl

TRIAVIL® 4-10: Each tablet contains
4 mg perphenazine and 10 mg amitriptyline HCl

INITIAL THERAPY FOR MANY PATIENTS
TRIAVIL® 2-25 (or TRIAVIL® 4-25) t.i.d. or q.i.d.

FOR FLEXIBILITY IN ADJUSTING MAINTENANCE THERAPY
TRIAVIL® 2-10 (or TRIAVIL® 4-10)

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. In patients with angle-closure glaucoma, even average doses may precipitate an attack. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either con uent alone.

Perphenazine: Side effects may be any of those reported w phenothiazine drugs: extrapyramidal symptoms (opisthotonus, c logyric crisis, hyperreflexia, dystonia, akathisia, acute dyskine ataxia, parkinsonism) can usually be controlled by the concomit use of effective antiparkinsonian drugs and/or by reduction in c age, but sometimes persist after discontinuation of the phenothiazir

Tardive dyskinesia may appear in some patients on long-term ti apy or may occur after drug therapy with phenothiazines and rela agents has been discontinued. The risk appears to be greater elderly patients on high-dose therapy, especially females. Sympto are persistent and in some patients appear to be irreversible. T syndrome is characterized by rhythmical involuntary movements the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing cheeks, puckering of mouth, chewing movements). Involuntary mo ments of the extremities sometimes occur. There is no known tre ment for tardive dyskinesia; antiparkinsonism agents usually do alleviate the symptoms. It is advised that all antipsychotic agents discontinued if the above symptoms appear. If treatment is reinst ted, or dosage of the particular drug increased, or another drug s stituted, the syndrome may be masked. It has been suggested t fine vermicular movements of the tongue may be an early sign of syndrome, and that the full-blown syndrome may not develop if me cation is stopped when lingual vermiculation appears.

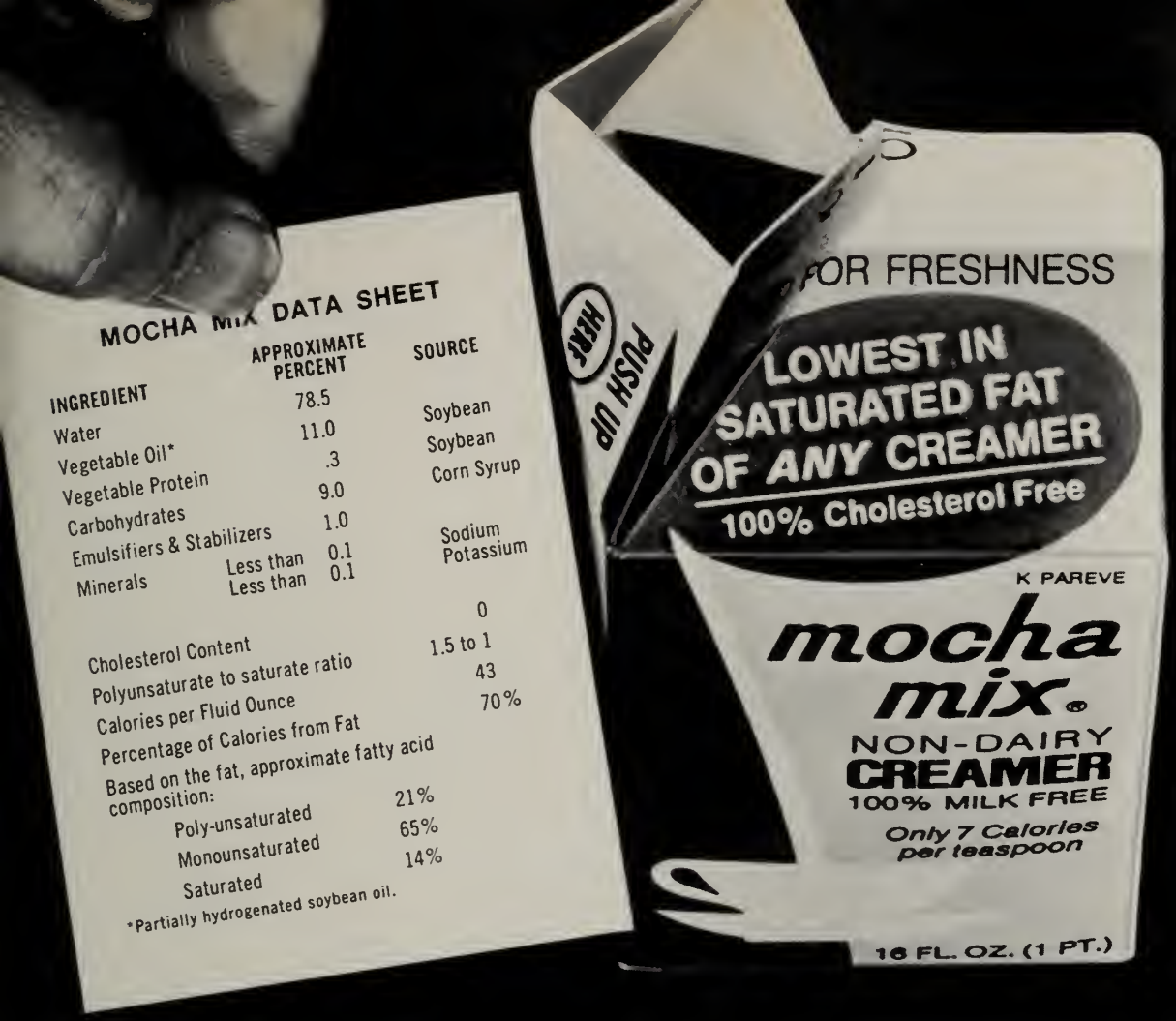
Other side effects are skin disorders (photosensitivity, itchi erythema, urticaria, eczema, up to exfoliative dermatitis); oth allergic reactions (asthma, laryngeal edema, angioneurotic ede anaphylactoid reactions); peripheral edema; reversed epinephr effect; hyperglycemia; endocrine disturbances (lactation, gal torrhea, gynecomastia, disturbances of menstrual cycle); alter cerebrospinal fluid proteins; paradoxical excitement; hypertensi hypotension, tachycardia, and ECG abnormalities (quinidine-l effect); reactivation of psychotic processes; catatonic-like stat autonomic reactions, such as dry mouth or salivation, headac anorexia, nausea, vomiting, constipation, obstipation, urina frequency or incontinence, blurred vision, nasal congestion, anc change in pulse rate; hypnotic effects; pigmentary retinopathy; c neal and lenticular pigmentation; occasional lassitude, muscle we ness, mild insomnia. Other adverse reactions reported with varic phenothiazine compounds include blood dyscrasias (pancytope thrombocytopenic purpura, leukopenia, agranulocytosis, eosinop ia); liver damage (jaundice, biliary stasis); grand mal convulsio cerebral edema; polyphagia; photophobia; skin pigmentation; a failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported this drug, but which have occurred with other pharmacologically si lar tricyclic antidepressant drugs. *Cardiovascular:* Hypotensi hypertension; tachycardia; palpitation; myocardial infarction; arrh mias; heart block; stroke. *CNS and Neuromuscular:* Confusio states; disturbed concentration; disorientation; delusions; halluci tions; excitement; anxiety; restlessness; insomnia; nightmares; nur ness, tingling, and paresthesias of the extremities; periphe neuropathy; incoordination; ataxia; tremors; seizures; alteration EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinerg* Dry mouth; blurred vision; disturbance of accommodation; consti tion; paralytic ileus; urinary retention; dilatation of urinary tra *Allergic:* Skin rash; urticaria; photosensitization; edema of face a tongue. *Hematologic:* Bone marrow depression including agran cytosis; leukopenia; eosinophilia; purpura; thrombocytopenia. *G trointestinal:* Nausea; epigastic distress; vomiting; anorex stomatitis; peculiar taste; diarrhea; parotid swelling; black tong *Endocrine:* Testicular swelling and gynecomastia in the male; bre enlargement and galactorrhea in the female; increased or decreas libido; elevated or lowered blood sugar levels. *Other:* Dizzine weakness; fatigue; headache; weight gain or loss; increased pers ration; urinary frequency; mydriasis; drowsiness; jaundice; alope *Withdrawal Symptoms:* Abrupt cessation after prolonged administ tion may produce nausea, headache, and malaise. These are r indicative of addiction.

OVERDOSAGE: All patients suspected of having taken an ov dosage should be admitted to a hospital as soon as possible. Tre ment is symptomatic and supportive. However, the intraveno administration of 1-3 mg of physostigmine salicylate has be reported to reverse the symptoms of tricyclic antidepressant pois ing. On this basis, in severe overdosage with perphenazine-a triptyline combinations, symptomatic treatment of centr anticholinergic effects with physostigmine salicylate should considered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

MSD
MERCK SHARP & DOHME



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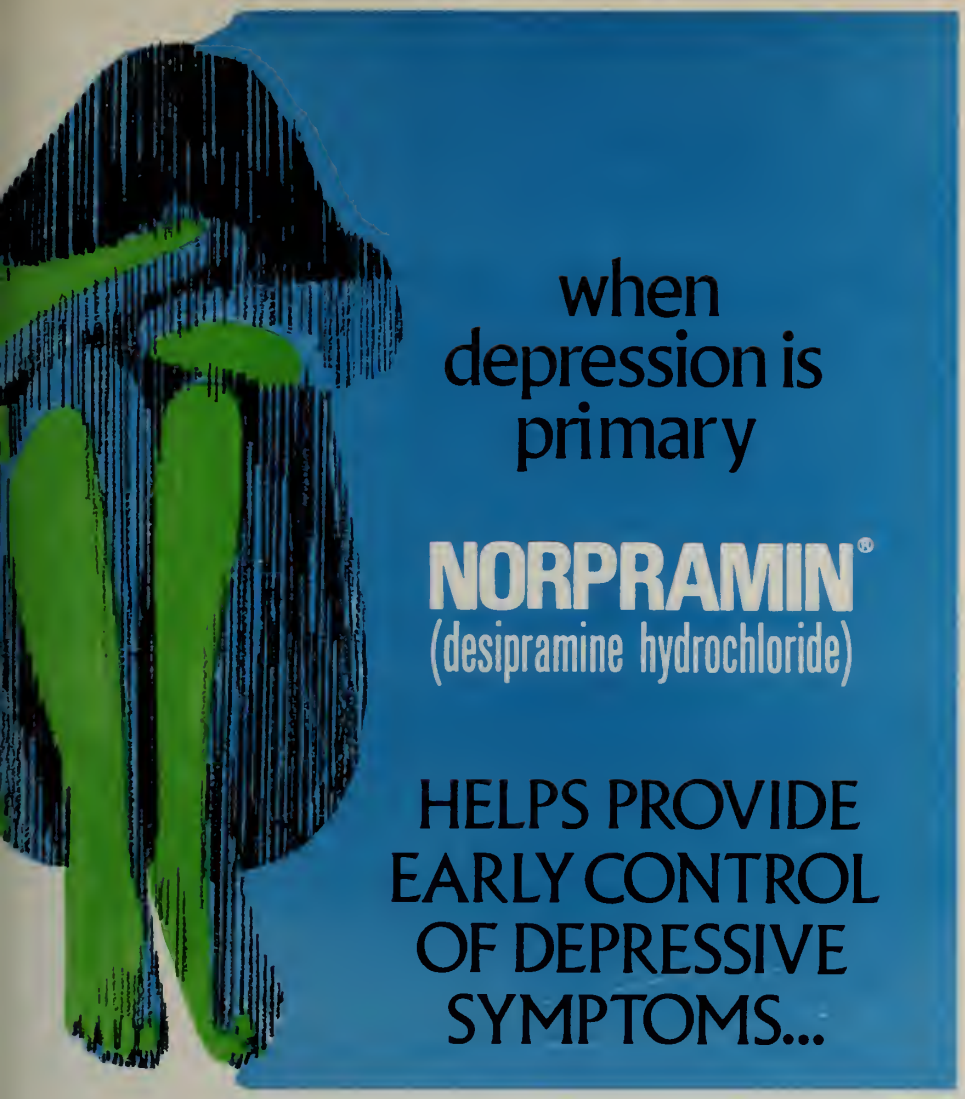
When you see anxiety-look for depression
NORPRAMI
(desipramine hydrochlorid



Anxiety is an invidious symptom. It feeds upon sickness, gnaws, grows and invades every cranny of psychic pathology adding intensity to torment. Anxiety as a symptom secondary to depression may be so dominant that it obscures the primary diagnosis. It may suggest treatment with tranquilizers which often help. But as the vampire of legend had to have a laurel stake driven through its heart to truly die, so anxiety secondary to depression will not cease to nibble and bite until an antidepressant eradicates the primary illness—and symptomatic anxiety starves.

IN BRIEF:

Indications: Norpramin® (desipramine hydrochloride) is indicated for the relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contraindications: Desipramine hydrochloride should not be given within two weeks of treatment with a monoamine oxidase inhibitor. Contraindications include the acute recovery period following myocardial infarction and hypersensitivity to the drug. Cross sensitivity with other dibenzazepines is a possibility.

Warnings: 1. Extreme caution should be used in patients: (a) with cardiovascular disease, (b) with a history of urinary retention or glaucoma, (c) with thyroid disease or those on thyroid medication, (d) with a history of seizure disorder. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. *Use in Pregnancy:* Safe use during pregnancy and lactation has not been established. 4. *Use in Children:* Norpramin® (desipramine hydrochloride) is not recommended for use in children. 5. This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Therefore, the patient should be cautioned accordingly.

Precautions: This drug should be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with drugs of this class. If possible, dispense in child-resistant containers. It should be kept out of reach of children. Reduce dosage, or alter treatment, if serious adverse effects occur. Norpramin® (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates and may cause exacerbation of phychosis in schizophrenic patients. Use cautiously with anticholinergic or sympathomimetic drugs. Response to alcoholic beverages may be exaggerated. In the concurrent administration of ECT and antidepressant drugs one should consider the possibility of increased risk relative to benefits. Discontinue as soon as possible prior to elective surgery because of possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is neutropenia.

Adverse Reactions: *Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. *Psychiatric:* confusional states (especially in the elderly), hallucinations, disorientation, delusions; anxiety, agitation; insomnia and nightmares; hypomania; exacerbation of phychosis. *Neurological:* paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, hypotonic bladder. *Allergic:* skin rash, petechiae, urticaria, itching, photosensitization, edema (of face and tongue or general), drug fever. *Hematologic:* agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue. *Endocrine:* gynecomastia; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels. *Other:* jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia. *Withdrawal Symptoms:* Though not indicative of addiction, abrupt cessation after prolonged therapy may produce nausea, headache and malaise.

Dosage and Administration: *The usual adult dose:* 50 mg. three times daily; increase if necessary after 7 to 10 days to maximum of 200 mg. daily. Dosages above 200 mg. per day are not recommended. *Maintenance:* At a lower dose adequate to maintain remission. *Adolescent and geriatric patient dose:* 25 to 50 mg. daily if necessary.

Overdosage: There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug. The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure and regulation of fluid- and acid-base balance are well known in most medical centers. If heart failure is imminent, digitalize promptly.

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CALIFORNIA
MEDICAL ASSOCIATION

104th Annual Session
AND
Western Scientific Assembly

February 21-26, 1975 • Los Angeles Convention Center • The Biltmore Hotel, Los Angeles

Registration Opens Friday, February 21, 7:45 a.m. at the Convention Center

(A booth will be open at the hotel from Saturday through Tuesday)

SCIENTIFIC SESSIONS	**Begin Friday Morning, February 21** **Conclude Monday, February 24** **Los Angeles Convention Center**	**HOUSE OF DELEGATES**	**Opening Session Saturday, February 22** **Closing Session Wednesday, February 26** **The Biltmore Hotel**

APPLICATION FOR HOTEL ACCOMMODATIONS

Fill in the form below **completely** for room accommodations at the CMA's 1975 Annual Session.

Your reservation request should include the definite date and hour of your arrival and departure.

All reservations, except for suites, must be made through The Biltmore Hotel, 515 South Olive Street, Los Angeles 90013 **by January 21, 1975.**

All SUITE reservations must be cleared through the CMA Convention Office, San Francisco. If you are requesting a suite, direct your requests to: CMA Convention Office, 731 Market Street, San Francisco 94103.

Cancellations: Please notify The Biltmore Hotel of all cancellations.

Changes: All other changes are also to be made directly with the hotel at all times.

THE BILTMORE HOTEL

Singles	$18-22
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Additional person in room	$ 4
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Send to: The Biltmore Hotel, Attn: Reservations
515 South Olive Street, Los Angeles 90013

Please reserve the following accommodations for the CMA's 1975 Annual Session:

Please Indicate Preference:

Single Bedroom $_____ Twin-Bed $_____ Double Bed $_____ Suite $_____

Arrival (date) _____ Hour _____ a.m. p.m. Departure (date) _____ Hour _____ a.m. p.m.

The name and address of each hotel guest must be listed. Include names and addresses of **each** person in a double or twin-bedded room, and names and addresses of **all other persons** for whom you are requesting reservations.

Your Name _____

Address _____ County _____

City and State _____ Zip Code _____

GUESTS' NAMES AND ADDRESSES:

_____

_____

_____

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IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparati should not be used. Antihistaminics appear beneficial in tr ment of procaine reaction.

The use of antibiotics may result in overgrowth of nons ceptible organisms. Constant observation of the patient is ess tial. If new infections due to bacteria or fungi appear dur therapy, discontinue penicillin and take appropriate measure

If allergic reaction occurs, withdraw penicillin unless, in opinion of the physician, the condition being treated is threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected prim or secondary syphilis, perform proper diagnostic procedu including darkfield examinations. In all cases in which conco tant syphilis is suspected, perform monthly serological tests fo least four months.

Adverse Reactions: (Penicillin has significant index of s sitization) skin rashes, ranging from maculopapular eruptions exfoliative dermatitis; urticaria; serum sickness-like reactic including chills, fever, edema, arthralgia and prostration. Sev and often fatal anaphylaxis has been reported. (See "Warnings.

As with other antisyphilitics, Jarisch-Herxheimer reaction l been reported.

Administration and Dosage: Administer only by *deep in muscular injection,* in upper outer quadrant of buttock. In infa and small children, midlateral aspect of thigh may be preferal When doses are repeated, vary injection site. Before injecti aspirate to be sure needle bevel is not in blood vessel. If blo appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have creased susceptibility to penicillin, this resistance is relative, absolute, and penicillin in large doses remains the drug of cho Physicians are cautioned not to use less than recommenc doses.

Gonorrheal infections (uncomplicated)—Men or Women: million units intramuscularly divided into at least two doses a injected at different sites at one visit, together with 1 gram of c probenecid, preferably given at least 30 minutes prior to injectic

NOTE: Treatment of severe complications of gonorrhea sho be individualized using large amounts of short-acting penicil Gonorrheal endocarditis should be treated intensively w aqueous penicillin G. Prophylactic or epidemiologic treatment gonorrhea (male and female) is accomplished with same tre ment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Ver real Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after thera In the male, a gram-stained smear is adequate if positive; oth wise, a culture specimen should be obtained from the anter urethra. In the female, culture specimens should be obtain from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persi 3 or more days following initial therapy and smear or cultu remains positive. Follow-up treatment consists of 4.8 million un I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment indicated if follow-up cervical or rectal cultures remain positive *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million un daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test syphilis at the time of diagnosis. Patients with gonorrhea w also have syphilis should be given additional treatment app priate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,0 units (4-cc. size) contains procaine penicillin G in a stabiliz aqueous suspension with sodium citrate buffer, and as w/v appro imately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% po vinylpyrrolidone, 0.01% propylparaben and 0.09% methylparabe The multiple-dose 10-cc. vial contains per cc. 300,000 units p caine penicillin G in a stabilized aqueous suspension with sodiu citrate buffer and approximately 7 mg. lecithin, 2 mg. carbo methylcellulose, 3 mg. polyvinylpyrrolidone, 0.5 mg. sorbit monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitat 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

N SYPHILIS
IJECTION
Bicillin® LONG-ACTING
STERILE BENZATHINE
ENICILLIN G
USPENSION) WYETH

yphilis is preferably treated with benzathine enicillin G, which is also the drug of choice r prophylaxis after exposure. Administra-on of 2.4 million units (1.2 million in each ittock) usually cures most cases of primary, condary and latent syphilis with negative inal fluid.

ndications: In treatment of infections due to penicillin ensitive microorganisms that are susceptible to the low and y prolonged serum levels common to this particular dosage n. Therapy should be guided by bacteriological studies (in-ding sensitivity tests) and by clinical response.
The following infections will usually respond to adequate age of intramuscular benzathine penicillin G.—Venereal in-tions: Syphilis, yaws, bejel and pinta.
FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any nicillin.

Warnings: Serious and occasionally fatal hypersensitivity (ana-ylactoid) reactions have been reported. Anaphylaxis is more quent following parenteral therapy but has occurred with oral nicillins. These reactions are more apt to occur in individuals h history of sensitivity to multiple allergens.
Severe hypersensitivity reactions with cephalosporins have en well documented in patients with history of penicillin hyper-sitivity. Before penicillin therapy, carefully inquire into pre-us hypersensitivity to penicillins, cephalosporins and other ergens. If allergic reaction occurs, discontinue drug and treat h usual agents, e.g., pressor amines, antihistamines and corti-steroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.
Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.
In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treat-ment to determine whether streptococci have been eradicated.
Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and ana-phylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associ-ated with high doses of parenteral penicillin.
As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—
Syphilis—Primary, secondary and latent—2.4 million units (1 dose).
Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.
Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdraw-ing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be pref-erable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

S Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

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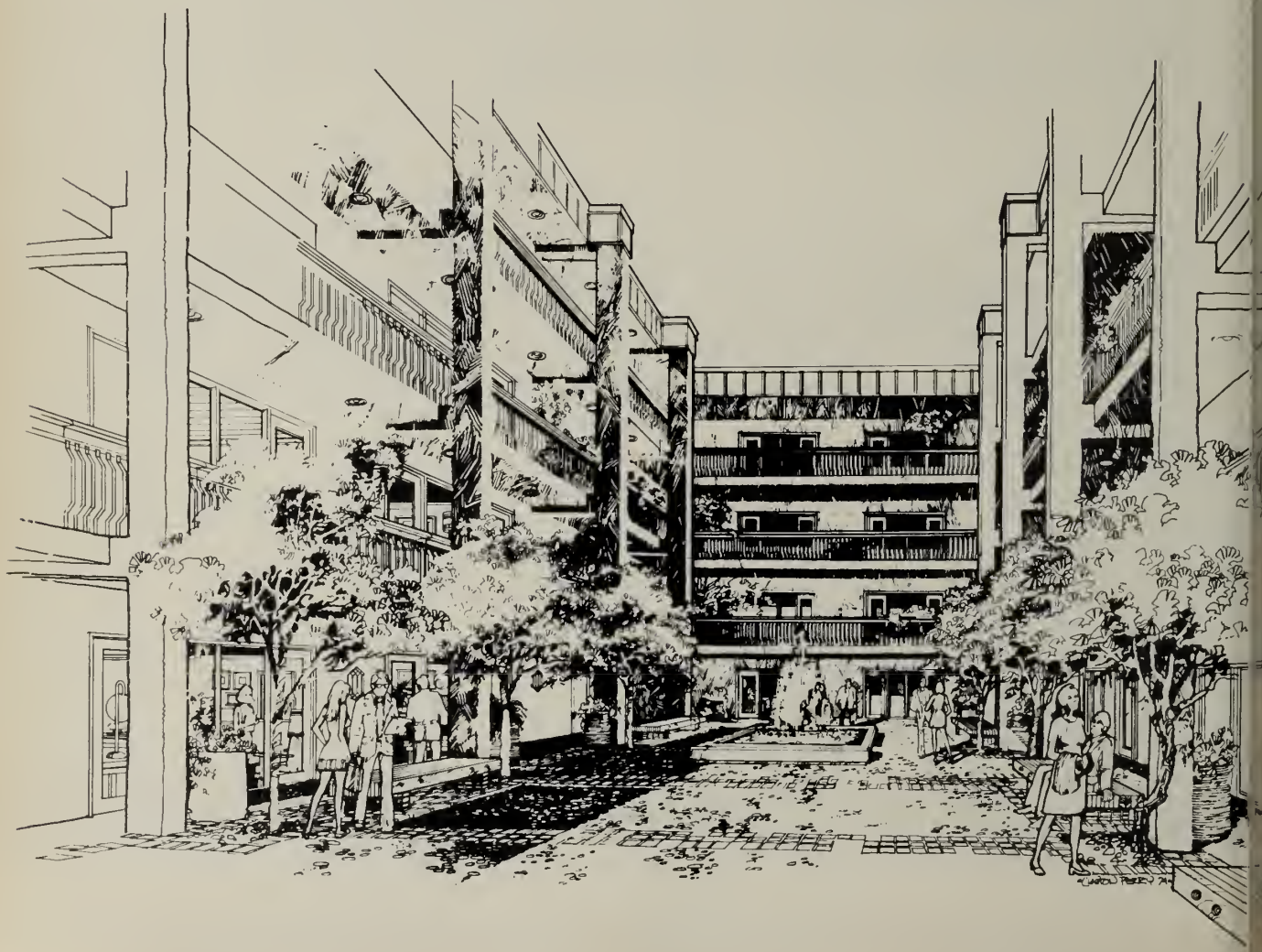

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

November 14-15—**Recent Advances in Hematology and Medical Oncology.** See Medicine, November 14-15.

November 15-16—**Current Concepts in the Diagnosis and Treatment of the Hidden Malignancies: The Intra-Abdominal Cancers.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. Contact: Dept. of Cont. Education, Mt. Zion Hospital, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 108.

November 23—**Breast Cancer: Update 1974.** American Cancer Society, N. E. Los Angeles County Unit, at Huntington-Sheraton Hotel, Pasadena. Saturday. 6 hrs. $20. Contact: Hilario R. Liras, Ed. Dir., ACS, 230 N. Lake Ave., No. 1, Pasadena 91101. (213) 795-7774.

December 8—**Slide Seminar on Tumors of the Gastro-Intestinal Tract.** California Tumor Tissue Registry at Century Plaza Hotel, Los Angeles. Sunday. Contact: Weldon K. Bullock, MD, Exec. Dir., Calif. Tumor Tissue Registry, L.A. County/USC Medical Ctr., 1200 N. State St., Box 40, L.A. 90033. (213) 225-3131, ext. 71820.

January 22—**Carcinoma of the Oral Cavity—Second Annual Central Valley Medical Conference.** American Cancer Society at Holiday Inn, Modesto. Wednesday. Contact Dr. Fredrick Mantz, P.O. Box 285, Modesto 95353. (209) 522-5238.

Continuously—**Tumor Conference.** Cruden Education Center, St. John's Hospital, Oxnard. Fridays, 12:00 noon-1:00 p.m. Advice and consultation from specialists in surgical, medical, radiotherapeutic, chemotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Cancer program has 3 year accreditation from American College of Surgeons. Contact: D. Gordon Johnston, MD, Dir. of Med. Ed., St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 266.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists (UCLA faculty members) in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John R. Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

November 13—**Great Issues of the Gut.** N. T. Enloe Memorial Hospital and Butte-Glenn Medical Society at Holiday Inn, Chico. Wednesday. Contact: Mr. John Behrman, Cont. Ed. Prog., N. T. Enloe Memorial Hospital, 5th Ave. & The Esplanade, Chico 95926.

November 14-15—**Recent Advances in Hematology and Medical Oncology.** UCLA at Holiday Inn, Los Angeles. Thursday-Friday.

November 16-17—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

November 17—**Veterinary Dermatology Seminar.** STAN. Sunday.

November 22—**Complications of Diabetes Mellitis—Pathophysiology and Management.** UCI at VA Hospital, Long Beach. Friday. 6 hrs.

November 23—**Update: Advances in Medical and Surgical Care of the Coronary Patient.** Inter-Hospital Council for Continuing Medical Education of the San Gabriel-Pomona Valleys at Kellogg West Conference Facility, Cal Poly, Pomona. Saturday. $60. Contact: Donald Adams, Admin., Foothill Presbyterian Hospital, Grand Avenue, Glendora 91740.

November 30-December 1—**Physiology of Respiration.** UCSF. Saturday-Sunday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

December 2-6—**Advances in Diagnosis and Treatment in Clinical Medicine.** American College of Physicians, UCLA, and Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Friday. $140 for ACP members; $200 non-members. Contact: ACP, Registrar, Postgraduate Courses, 4200 Pine St., Philadelphia, Pa. 19104. (215) 222-8120.

December 5-7—**Advances in Heart Disease 1975.** American College of Cardiology at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

December 7—**Seminar on the Practical Aspects of Blood Banking.** UCLA. Saturday.

December 11—**Colloquia in Cardiology—No. 7: Echocardiography.** American College of Cardiology at Ambassador Hotel, Los Angeles. Wednesday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

December 11-13—**Exercise and Coronary Disease.** USC at Sheraton-Waikiki Hotel, Honolulu. Wednesday-Friday.

December 14-15—**Kidney Function.** UCSF. Saturday-Sunday.

December 15—**Advances in Diagnosis and Treatment in Clinical Medicine.** UCLA and Granada Community Hospital at Calif. State Univ., Northridge. Sunday. Contact: Rose Degraffenreid, Granada Community Hospital, 10445 Balboa Blvd., Granada Hills 91344. (213) 360-1021, ext. 730.

January 8—**Pediatric Dermatology.** See Pediatrics, January 8.

January 16-18—**The Respective Roles of Medicine and Surgical Treatment in Cardiac Disease in the Adult.** American College of Physicians, UCLA, Cedar-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Thursday-Saturday. $100 for ACP members; $150, non-members. Contact: Registrar, Postgraduate Courses, 4200 Pine St., Philadelphia, Pa. 19104. (215) 222-8120.

January 17-18—**Colonoscopy.** American and Southern Calif. Societies for Gastrointestinal Endoscopy at Beverly Hilton Hotel, Bevery Hills. Friday-Saturday. 9 hrs. $65 for members; $90, non-members. Contact: Melvin Schapiro, MD, 5400 Balboa Blvd., No. 202, Encino 91316. (213) 981-1300.

January 24-25—**Medical Application of Behavior Modification.** See Psychiatry, January 24-25.

January 26-February 1—**Skiers' Symposium: Pre-, Intra- and Post-Operative Management of the Surgical Patient.** See Of Interest To All, January 26-February 1.

January 29—**Pediatric Dermatology.** See Pediatrics, January 29.

January 29-31—**Pediatric Dermatology.** See Pediatrics, January 29-31.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Cardiology Conferences.** Samuel Merritt Hospital, Oakland. First and third Mondays, 12:00 noon-1:30 p.m., Classroom No. 9. Reviews and case discussions on selected topics of current interest in cardiology. Luncheon served. Contact: Thomas P. Forde, MD, 3326 Webster St., Oakland 94609.

(Continued on Page 47)

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing wit prescription.
Description. Proloid (thyroglobulin) is obtai from a purified extract of frozen hog thyr It contains the known calorigenically ac components, Sodium Levothyroxine (T_4) Sodium Liothyronine (T_3). Proloid (thyroglo lin) conforms to the primary USP specificati for desiccated thyroid—for iodine based chemical assay—and is also biologically sayed and standardized in animals.
Chromatographic analysis to standardize Sodium Levothyroxine and Sodium Liothy nine content of Proloid (thyroglobulin) is r tinely employed.
The ratio of T_4 and T_3 in Proloid (thyrogl ulin is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when sto at usual room temperature.
Indications. Proloid (thyroglobulin) is thyr replacement therapy for conditions of ina quate endogenous thyroid production: e cretinism and myxedema. Replacement ther will be effective only in manifestations of hy thyroidism.
In simple (nontoxic) goiter, Proloid (thy globulin) may be tried therapeutically, in n emergency situations, in an attempt to red the size of such goiters.
Contraindication. Thyroid preparations contraindicated in the presence of uncorrec adrenal insufficiency.
Warnings. Thyroglobulin should not be us in the presence of cardiovascular disease less thyroid-replacement therapy is clearly dicated. If the latter exists, low doses sho be instituted beginning at 0.5 to 1.0 grain to 64 mg) and increased by the same amo in increments at two-week intervals. This mands careful clinical judgment.
Morphologic hypogonadism and nephro should be ruled out before the drug is adm istered. If hypopituitarism is present, the ad nal deficiency must be corrected prior starting the drug.
Myxedematous patients are very sensitive thyroid and dosage should be started at a v low level and increased gradually.
Precaution. As with all thyroid preparatio this drug will alter results of thyroid funct tests.
Adverse Reactions. Overdosage or too ra increase in dosage may result in signs a symptoms of hyperthyroidism, such as me strual irregularities, nervousness, cardiac rhythmias, and angina pectoris.
Dosage and Administration. Optimal dosa is usually determined by the patient's clini response. Confirmatory tests include BMR, ^{131}I resin sponge uptake, T_3 ^{131}I red cell u take, Thyro Binding Index (TBI), and Achil Tendon Reflex Test. Clinical experience h shown that a normal PBI (3.5-8 mcg/100 r will be obtained in patients made clinic euthyroid when the content of T_4 and T_3 adequate. Dosage should be started in sm amounts and increased gradually with inc ments at intervals of one to two weeks. Us maintenance dose is 0.5 to 3.0 grains (32 190 mg) daily.
Overdosage Symptoms. Headache, instabili nervousness, sweating, tachycardia, with u usual bowel motility. Angina pectoris or co gestive heart failure may be induced aggravated. Shock may develop. Massive ov dosage may result in symptoms resembli thyroid storm. Chronic excessive dosage produce the signs and symptoms of hyperth roidism.
(Treatment: In shock, supportive measur should be utilized. Treatment of unrecogniz adrenal insufficiency should be considered.)
How Supplied. ¼ grain; ½ grain; scored grain; 1½ grain; scored 2 grain; 3 grain; a scored 5 grain tablets, in bottles of 100 a 1000.
Full information available on request.
WARNER/CHILCOTT
Division, Warner-Lambert Company
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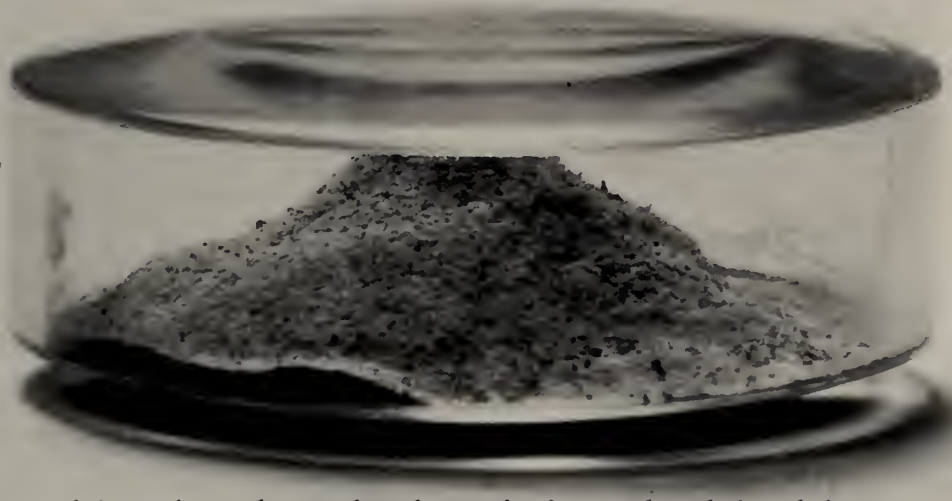
PR-GP-31-B/W

IN NATURAL THYROID THERAPY:

ARE PATIENTS GETTING THE POTENCY YOU PRESCRIBE?



Unlike U.S.P. desiccated thyroid, Proloid®(thyroglobulin) offers the assurance of constant potency.

To begin with, Proloid is uniquely purified. The thyroglobulin extracted from hog thyroid is devoid of any glandular debris.

Then, Proloid is chemically and biologically assayed to assure consistent metabolic activity from batch to batch. The T_4 and T_3 content of every dose is blended for optimal thyroid replacement.

Important, too, is the fact that Proloid is invariably "fresh" when your patients take it. Under proper storage conditions, its potency will not diminish for at least four years.

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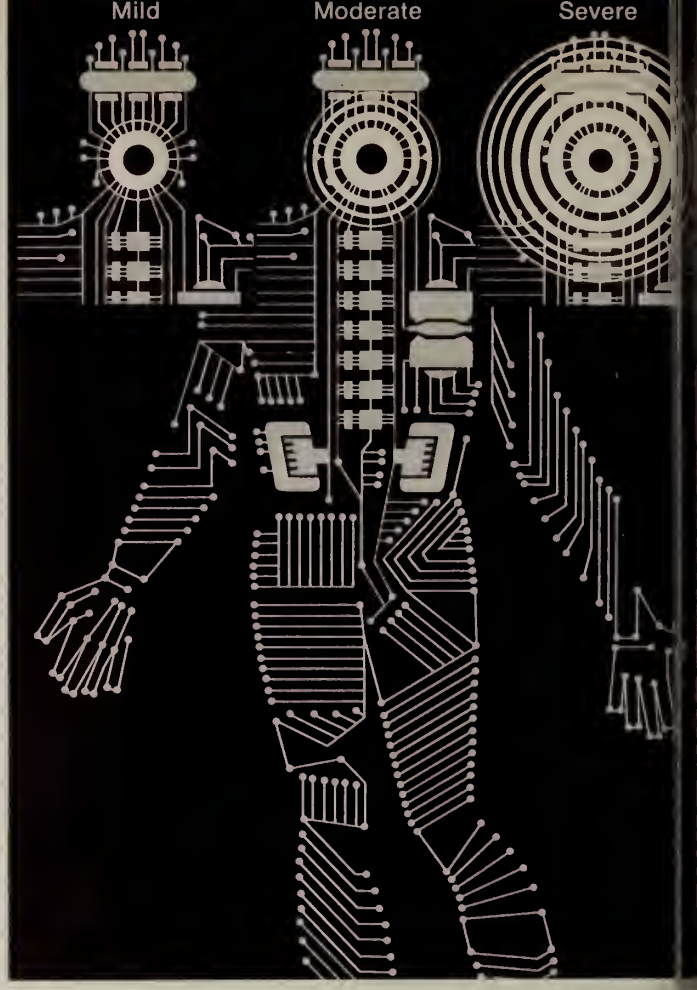
PROLOID®
(thyroglobulin)

natural thyroid therapy that leaves nothing to chance

Catapres Man. He can handle hypertension, from mild to severe



Catapres is effective in mild to severe hypertension. It is n
to moderate in potency. Its effectiveness is enhanced in c
bination with a diuretic such as chlorthalidone.

The table shows some representative results on the eff
tiveness of new Catapres, with and without chlorthalidone
in hypertension from mild to severe.

Try new Catapres. Alone. Or in combination with other
hypertensive agents. Because *how* you lower blood press
can make a difference.

Blood pressure responses to Catapres alone or in combination with a diuretic, as shown in three controlled studies[1-3]

Investigator	No. of patients	Author's description of degree of hypertension	Mean blood pressure (mm Hg) in recumbent position		
			Control	Catapres alone	Catapre a diur
Putzeys and Hoobler[1]	12	moderately severe	173/106		143/9
Elkeles *et al.*[2]	9	mild to moderate	182/110	159/95	
Finnerty, Mroczek *et al.*[3]	41	moderate to severe	176/116*		143/9

*Sitting blood pressure.

new Catapres
(clonidine hydrochloride)

Tablets of 0.1 and 0.2 mg

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Elmsford, New York 10523

Please see adjoining co
for brief summary of
prescribing information

ew Catapres®
clonidine hydrochloride)

blets of 0.1 mg and 0.2 mg
lication: The drug is indicated in the treatment of hyperten-
n. As an antihypertensive drug, Catapres (clonidine hydro-
loride) is mild to moderate in potency. It may be employed in
general treatment program with a diuretic and/or other antihy-
rtensive agents as needed for proper patient response.
rnings: Tolerance may develop in some patients necessitating
eevaluation of therapy.
age in Pregnancy: In view of embryotoxic findings in animals,
d since information on possible adverse effects in pregnant
men is limited to uncontrolled clinical data, the drug is not
commended in women who are or may become pregnant unless
potential benefits outweigh the potential risk to mother
d fetus.
age in Children: No clinical experience is available with the
e of Catapres (clonidine hydrochloride) in children.
ecautions: When discontinuing Catapres (clonidine hydro-
oride), reduce the dose gradually over 2 to 4 days to avoid
ossible rapid rise in blood pressure and associated sub-
tive symptoms such as nervousness, agitation, and headache.
tients should be instructed not to discontinue therapy with-
consulting their physician. Rare instances of hypertensive
cephalopathy and death have been recorded after cessation of
nidine hydrochloride therapy. A causal relationship has not
en established in these cases. It has been demonstrated that
excessive rise in blood pressure, should it occur, can be
ersed by resumption of clonidine hydrochloride therapy or
intravenous phentolamine. Patients who engage in potentially
zardous activities, such as operating machinery or driving,
ould be advised of the sedative effect. This drug may enhance
CNS-depressive effects of alcohol, barbiturates and other
datives. Like any other agent lowering blood pressure, cloni-
e hydrochloride should be used with caution in patients with
vere coronary insufficiency, recent myocardial infarction,
rebrovascular disease or chronic renal failure.
As an integral part of their overall long-term care, patients
ated with Catapres (clonidine hydrochloride) should receive
riodic eye examinations. While, except for some dryness of
eyes, no drug-related abnormal ophthalmologic findings have
en recorded with Catapres, in several studies the drug pro-
ced a dose-dependent increase in the incidence and severity
spontaneously occurring retinal degeneration in albino rats
ated for 6 months or longer.
verse Reactions: The most common reactions are dry mouth,
owsiness and sedation. Constipation, dizziness, headache, and
igue have been reported. Generally these effects tend to
minish with continued therapy. The following reactions have
en associated with the drug, some of them rarely. (In some
tances an exact causal relationship has not been established.)
ese include: Anorexia, malaise, nausea, vomiting, parotid pain,
ld transient abnormalities in liver function tests; one report of
ssible drug-induced hepatitis without icterus and hyperbili-
binemia in a patient receiving clonidine hydrochloride, chlor-
alidone and papaverine hydrochloride.
Weight gain, transient elevation of blood glucose, or serum
eatine phosphokinase; congestive heart failure, Raynaud's
enomenon; vivid dreams or nightmares, insomnia, other be-
vioral changes, nervousness, restlessness, anxiety and mental
pression. Also rash, angioneurotic edema, hives, urticaria,
nning of the hair, pruritus not associated with a rash, impo-
nce, urinary retention, increased sensitivity to alcohol, dryness,
hing or burning of the eyes, dryness of the nasal mucosa, pallor,
necomastia, weakly positive Coombs' test, asymptomatic elec-
cardiographic abnormalities manifested as Wenckebach period
ventricular trigeminy.
erdosage: Profound hypotension, weakness, somnolence, di-
nished or absent reflexes and vomiting followed the accidental
estion of Catapres (clonidine hydrochloride) by several chil-
n from 19 months to 5 years of age. Gastric lavage and ad-
nistration of an analeptic and vasopressor led to complete
covery within 24 hours. Tolazoline in intravenous doses of
mg at 30-minute intervals usually abolishes all effects of
tapres (clonidine hydrochloride) overdosage.
w Supplied: Catapres, brand of clonidine hydrochloride, is
ailable as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored
blets in bottles of 100.
For complete details, please see full prescribing information.
Under license from Boehringer Ingelheim GmbH

ferences: 1. Putzeys, M. R. and Hoobler, S. W.: Comparison
clonidine and methyldopa on blood pressure and side effects
hypertensive patients, Am. Heart J. 83:464, 1972. 2. Elkeles,
S., Goldby, F. S. and Oliver, D. O.: A Double Blind Study of
tapres, A New Antihypertensive Agent, in Conolly, M. E. (ed.):
apres in Hypertension, London, Butterworths, 1970, pp. 139-
. 3. Mroczek, W. J., Leibel, B. A. and Finnerty, F. A., Jr.:
mparison of clonidine and methyldopa in hypertensive patients
eiving a diuretic, Am. J. Cardiol. 29:712, 1972.

(Continued from Page 44)

Continuously—**Cardiology Conference/General Medical Conference.** Cruden Education Center, St. John's Hospital, Oxnard. Tuesdays, 12:00 noon-1:00 p.m. Conferences including case presentations, discussions of specific cardiology and medical problems. Contact: R. E. Liguori, MD, Dir. of Cardiovascular Laboratory, St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 256.

Continuously—**Cardiology Conferences.** San Diego County Heart Association at Sharp Hospital, San Diego. Fridays, 8-10 a.m. Contact: William Kuzman, MD, Sharp Hospital, 7901 Frost St., San Diego. (714) 277-6121. Or Mrs. Cathy Ware, SDCHA, P.O. Box 3625, San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 294-5663. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conference.** Thursdays, 8:00 p.m. **Cardiosurgical Conference.** Fridays, 2:00 p.m. UCSD at University Hospital, San Diego.

Continuously—**Medical Mortality Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Fridays, 11:30 a.m.

Continuously—**Medical Chest Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

Continuously—**Medical-Surgical G.I. Conference.** UCSD at University Hospital, 3rd floor, rm 3, San Diego. Tuesdays, 12:30 p.m.

Continuously—**Hematology Pathology/Hematology Morphology Conference.** Mondays, 11:00 a.m. **Hematology Clinical Conference.** Mondays, 12 noon. UCSD alternating between University and VA Hospitals, San Diego.

Continuously—**Gastroenterology Conference.** Tuesdays, 11:00 a.m. **Gastrointestinal Conference.** Tuesdays, 12:30 p.m. **Gastroenterology-Pathology Conference.** Wednesdays, 11:00 a.m. UCSD at University Hospital, San Diego.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Preceptorships in Cardiology.** PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Continuously—**Preceptorships in Practical Office Dermatology.** PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Continuously—**Preceptorships in Infectious Disease.** PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Renal Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

Continuously—**Rheumatology Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. 2nd and 4th Fridays, 12:30 p.m.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of every other month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1534.

Continuously—**Training for Physicians in General Internal Medicine.** LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Dermatology. 11:00 a.m. VA Hospital, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

8:30 a.m., Auditorium, Brown Bldg., Mt. Sinai Hospital, Los Angeles. UCLA.

Dermatology. 10:00 a.m. University Hospital, San Diego. UCSD.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:00 noon. Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., VA Hospital, San Diego. UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UC

8:00-10:00 a.m., 4th Floor, UCLA Medical Center. UCL

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Die County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conf ence room, Huntington Intercommunity Hospital, Hunti ton Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County Gene Hospital, Bakersfield. UCLA.

8:30-10:00 a.m., Auditorium, Lebanon Hall, Cedars Lebanon Hospital, Los Angeles. UCLA. Second a Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford Univ sity Hospital and Neurology Conference Building 7, Hospital, Palo Alto. STAN.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p. Staff Room, St. Mary's Long Beach Hospital, Long Bea

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1: p.m., Staff Room, St. Mary's Long Beach Hospital, Lo Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Resea Bldg., La Jolla. Scripps Clinic and Research Foundati

Rheumatology. 11:45 a.m., Room 6441, Los Ange County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

November 22-25—**1974 Symposium of Gynecologic Endosco** American Association of Gynecological Laparoscopists Disneyland Hotel, Anaheim. Friday-Monday. Contact: J dan M. Phillips, MD, 11239 S. Lakewood Blvd., Dow 90241. (213) 862-8181.

December 2-6—**Family Planning.** UCLA. Monday-Frid Contact: Irvin M. Cushner, MD, Ob-Gyn Dept., UC Center for Health Sciences, L.A. 90024. (213) 825-1046.

January 27-28—**Neonatal Respiratory Symposium.** USC Marriott Hotel, Los Angeles. Monday-Tuesday. Will rec vene in Aspen, Colo., January 29-31. Contact: John S. Donald, MD, Dir., Perinatal Anesthesia, P.O. Box 545 Los Angeles 90054.

January 27-30—**Perinatal Medicine.** USC at Kona Surf Ho Kona, Hawaii. Monday-Thursday. $180.

Continuously—**Ob-Gyn Case Review.** Saturdays, 8:00 a.m. **Tumor Conference/Mortality Conference.** Wednesda 12:30 p.m. **Ob-Gyn Pathology Conference.** Wednesdays, 4 p.m. UCSD at University Hospital, San Diego.

Continuously—**Ob/Gyn Conference.** San Joaquin General H pital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' D ing Room. Contact: J. D. Kortzeborn, MD, Med. Dir., Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** Mary's Hospital, San Francisco. See Radiology and Pat ogy, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10:30 a.m., Assembly Room, First Floor, Harbor G eral Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, L

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Cen Sacramento. UCD.

8:00-9:00 a.m., Fourth Floor Auditorium, UCLA Medical Center. UCLA.

5:00 p.m. Pickard Auditorium, University Hospital, San Diego. UCSD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

EDIATRICS

)ecember 7—**American Academy of Pediatrics, Chapter I, District IX.** San Franciscan-PSA Hotel, San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501. (415) 523-3417.

ınuary 8—**Pediatric Dermatology.** USC at Womens Hospital, Los Angeles. Wednesday.

ınuary 14-15—**Adolescent Medicine.** USC. Tuesday-Wednesday.

ınuary 24-26—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 24-26.

ınuary 29—**Pediatric Dermatology.** USC at Womens Hospital, Los Angeles. Wednesday.

ınuary 29-31—**Pediatric Dermatology.** STAN and American Academy of Pediatrics at Holiday Inn, Palo Alto. Wednesday-Friday.

ınuary 30—**The Battered Child.** USC at Casa Royal, Bakersfield. Thursday.

ontinuously—**Fellowship in Cleft Palate.** See Surgery, Continuously.

ontinuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

ontinuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

ontinuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

ontinuously—**Pediatric Cardiology Conference.** UCSD. Small Conference Room, University Hospital, San Diego. Fridays, 12:30 p.m.

ontinuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., and Fridays, 9:30-11:00 a.m., Conference Room 3. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ontinuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ontinuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Fourth Thursday of each month, 2:00 p.m., Main Doheny Conference Room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

ontinuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

RECENT ADVANCES IN

NEUROLOGY

JANUARY 29-31, 1975

Cole Hall, Medical Science Building
University of California
San Francisco, California

Presented by
DEPARTMENT OF NEUROLOGY
UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE

In cooperation with
EXTENDED PROGRAMS IN MEDICAL EDUCATION
UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE
San Francisco, California

The emphasis of this course is on what is *NEW* in clinical neurology.

The *first day* of the program includes the *Sandoz Headache Symposium* for which *Doctors Arnold P. Friedman*, University of Arizona, Tucson, Arizona and *Donald Dalessio*, Scripps Clinic and Research Foundation, La Jolla, California will present talks.

The *other subjects* covered this year include

- **VISUAL-EVOKED RESPONSE**
- **SPINAL VASCULAR MALFORMATIONS**
- **BRAIN EDEMA**
- **DRUG-INDUCED COMA**
- **ADVANCES IN THE TREATMENT OF EPILEPSY**
- **THE MOYA MOYA SYNDROME**
- **POST-SYMPATHECTOMY NEURALGIA**
- **COMPUTERIZED TOMOGRAPHIC (EMI) SCANNING**
- **NEUROLOGY OF ORGAN TRANSPLANTATION**

Doctor Gilbert Glaser, Yale University School of Medicine, New Haven, Connecticut with Doctors Friedman and Dalessio will complete the visiting faculty roster.

The *remainder of the course faculty* is derived from University of California, San Francisco, California. Neurologists, neurosurgeons, internists, pediatricians, generalists, and psychiatrists will find the sessions of interest. It is acceptable for *14½ hours Category 1 Credit* towards the certificate in Continuing Education for the American Medical Association and the California Medical Association.

REGISTRATION FEE IS $100 (includes lunch); HALF FEE for non-UC residents with letter of verification. REGISTRATION IN ADVANCE IS ADVISED. $10 FEE for refunds requested before course; NO REFUNDS after course begins.

Check should be made payable to the
REGENTS OF THE UNIVERSITY OF CALIFORNIA
c/o Extended Programs in Medical Education
Room 575-U
University of California
San Francisco, CA 94143.

For Registration Information call (415) 666-2483
For Program Information call (415) 666-4251

Continuously—**Pediatric Immunology and Allergy Seminar.** UCSD. Wednesdays, 8:00 a.m.

Continuously—**Pediatric Neurology.** UCSD at University Hospital, 3rd floor, rm. 3, San Diego. 1st and 3rd Wednesdays, 12:30 p.m.

Continuously—**Pediatric-Radiology-Urology Conference.** UCSD at University Hospital, Radiology Conference Room, San Diego. 1st and 3rd Fridays, 4:00 p.m.

Grand Rounds—Pediatrics

Tuesdays

Pediatric Cardiology. 7:30 a.m. University Hospital, San Diego. UCSD.

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Pediatric Infectious Disease. 1:30 p.m. University Hospital, San Diego. UCSD.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:30 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., 5th floor Ward, St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

December 2-7—**Psychiatry and Civil Law.** USC. Monday-Saturday. $175. Contact: Seymour Pollack, MD, Dir., USC Institute of Psychiatry, Law and Behavioral Science, 2025 Zonal Ave., L.A. 90033. (213) 226-4942.

December 13—**Psychological Aspects of the Rehabilitation of Patients with Industrial Back Injuries.** PMC. Friday.

January 15-April 2—**Advanced Psychotherapeutic Techniques —A Practical Approach to Therapy.** UCLA. Wednesday evenings; 12 sessions.

January 24-25—**Medical Application of Behavior Modificat** PMC. Friday-Saturday.

January 25-26—**Autism: Diagnosis, Current Research and M agement.** UCLA. Saturday-Sunday.

Continuously—**Adolescent Case Review.** St. Mary's Hosp San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Con ence Room. Contact: Charles H. Lithgow, MD, Dir. of M cal Education, St. Mary's Hospital, 2200 Hayes St., San Fr cisco 94117. (415) 752-4000.

Continuously—**Seminar in Ambulatory Methods.** UCSD Mental Health Clinic, San Diego. Mondays, 11:00 a.m.

Continuously—**Preceptorships in Psychiatry.** UCSF. By rangement.

Grand Rounds—Psychiatry

Tuesdays

8:30 a.m. VA Hospital, Rm. 2010, San Diego. UCSD

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacrame UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, Francisco.

RADIOLOGY AND PATHOLOGY

November 16-17—**American Association for Electromyogra and Electrodiagnosis.** St. Francis Hotel, San Francisco. urday-Sunday. Contact: W. C. Wiederholt, MD, Sec., 7 Via Valverde, La Jolla 92037. (714) 459-8443.

January 6-7—**The Hemoglobinopathies—Their Manifestati and Laboratory Diagnosis.** Memorial Hospital Medical C ter of Long Beach-UCI Center for Health Education Am. Soc. of Clinical Pathologists. Monday-Tuesday. $1 Contact: Exec. Sec., Ctr. for Health Education, 2801 lantic Ave., Long Beach 90801. (213) 595-3823.

January 26-28—**Genitourinary Pathology.** UCI at Memo Hospital Medical Center, Long Beach. Sunday-Tuesday.

January 31-February 2—**Los Angeles Midwinter Radiolog Conference—27th Annual.** Los Angeles Radiological Soc at Century Plaza Hotel, Los Angeles. Friday-Sunday. C tact: James F. Mack, MD, St. Mary's Hospital, 509 E. 1 St., Long Beach 90813.

Continuously—**Nuclear Medicine Conference.** Radiology Cl room, St. John's Hospital, Oxnard. Mondays, 12:00 no 1:00 p.m. Cases reviewed and discussed. Advice and con tation from specialists in the practice of nuclear medic techniques. Contact: Michael Lopiano, MD, Dir. of Nucl Med. Dept., St. John's Hospital, 333 N. "F" St., Oxn 93030. (805) 483-1141, ext. 297.

Continuously—**Ob/Gyn Correlated Pathology Conference.** Mary's Hospital, San Francisco. Mondays, 12:00 noon, S Lounge. Contact: Charles H. Lithgow, MD, Dir. of Med Education, St. Mary's Hospital, 2200 Hayes St., San Fr cisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's H pital, San Francisco. 2nd and 4th Wednesdays. Cont Charles H. Lithgow, MD, Dir. of Medical Education, Mary's Hospital, 2200 Hayes St., San Francisco 94117. (4 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Fr cisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room Contact: Charles H. Lithgow, MD, Dir. of Medical Ed tion, St. Mary's Hospital, 2200 Hayes St., San Franci 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's H pital, San Francisco. Third Tuesday of each month, 9: 10:00 a.m., Morrissey Hall. Contact: Charles H. Lithg

MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward I. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses ot radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Continuously—**Medical X-Ray Conference.** Monday-Friday, 9:30 a.m. (Wednesdays, 8:30 a.m.). **Diagnostic X-Ray Review.** Wednesdays, 3:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Radiology/Pathology Conference.** UCSD at University Hospital, Pickard Amphitheatre, San Diego. Thursdays, 12:30 p.m.

Continuously—**G.I. Radiology Conference.** Fridays, 1:00 p.m. **Pediatric Radiology Conference.** Thursdays, 4:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Neuroradiology Conference.** UCSD at University Hospital, San Diego, Tuesdays, 4:30 p.m. and at VA Hospital, San Diego, Wednesdays, 2:00 p.m.

Continuously—**Ortho-Radiology Conference.** UCSD at VA Hospital, San Diego. Fridays, 8:00 a.m.

Continuously—**Radiology-Urology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 3:30 p.m.

Continuously—**Pathology Review.** Wednesdays, 9:30 a.m. **Cardiovascular Pathology Conference.** Tuesdays, 8:00 a.m. **Pathology-Urology Conference.** Alternate Mondays, 4:30 p.m. UCSD at University Hospital, San Diego.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

November 14-15—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

November 14-16—**Phaco-Emulsification.** St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

November 16—**Intraocular Lens Implant Conference—Current Status and Analysis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. $100. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

November 16-17—**American Society of Anesthesiologists—Regional Refresher Course.** Riviera Hotel, Palm Springs. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068.

November 20-23—**Western Surgical Association—Annual Meeting.** Union Square Hyatt, San Francisco. Wednesday-Saturday. Contact: William P. Mikkelson, MD, 1127 Wilshire Blvd., Los Angeles 90017.

November 21-23—**Management of Acute Hand Injuries.** USC and American Academy of Orthopaedic Surgeons at USC. Thursday-Saturday. Contact: USC or Arthur H. Osborne, MD, 3314 Rancho Rio Bonita Rd., Covina 91724.

November 23—**Anesthesia Postgraduate Seminar—Pain, Drug Abuse and Their Management.** UCD at Woodlake Inn, Sacramento. Saturday.

November 23—**Update: Advances in Medical and Surgical Care of the Coronary Patient.** See Medicine, November 23.

December 4-6—**Advise and Dissent in Glaucoma—Annual Ophthalmology Course.** UCSF at Union Square Hyatt, San Francisco. Wednesday-Friday.

December 6-8—**Electronystagmography.** PMC at Sheraton Palace Hotel, San Francisco. Friday-Sunday.

APPLIED NUTRITION—BEGINNING COURSE

Course No. 43-75

CARLTON FREDERICKS, PhD

JANUARY 11, 12, 1975 • 9:00 A.M. TO 5:00 P.M.

Tuition:

$100—Doctors
$ 50—Dental Hygienists
$ 30—Dental Assistants or Spouse

CLINICAL PATHOLOGY OF THE ORAL MUCOSA

Course No. 81-75

RAYMOND J. MELROSE, DDS
ALBERT M. ABRAMS, DDS, MS

JANUARY 25, 1975 • 9:00 A.M. TO 5:00 P.M.

Tuition:

$ 55—Doctors
$ 35—Dental Hygienists
$ 20—Dental Assistants or Spouse

Please make checks payable to the University of Southern California and mail to the University of Southern California, School of Dentistry, Continuing Education, 925 W. 34th St., Los Angeles, California 90007. For further information, write to above address or telephone (213) 746-2845.

December 11-14—**Fluorescein Angiography and Photocoagulation in Macular and Retinal Vascular Disease.** USC. Wednesday-Saturday.

December 12-13—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

December 12-14—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

December 14—**Orthopaedic Surgery and Surgical Anatomy of the Neck and Upper Extremity.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. $50. 8 hrs. Contact: Irving Rehman, PhD, Chairman, Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

January 6-10—**Anesthesiology 1975.** Anesthesiology Education Foundation and Calif. Soc. of Anesthesiologists at Mammoth Mountain Inn, Mammoth Lakes. Monday-Friday. $175. Contact: Richard W. Patterson, MD, Dept. of Anesthesiology, UCLA. (213) 825-5021.

January 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

January 13-17—**Intensive Course in Otologic Surgery.** Ear Research Institute, USC, St. Vincent's Hospital at Ear Research Institute, Los Angeles. Monday-Friday. $500; $200 for residents. Contact: Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

January 16-18—**The Respective Roles of Medical and Surgical Treatment in Cardiac Disease in the Adult.** See Medicine, January 16-18.

January 17-18—**Colonoscopy.** See Medicine, January 17-18.

January 19—**Orthopaedic Surgery and Surgical Anatomy of the Wrist and Hand.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital, Los Angeles. Sunday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

January 20-23—**Midwinter Clinical Convention for Ophthalmology and Otolaryngology.** The Research Study Club of Los Angeles, Inc., at Hilton Hotel, Los Angeles. Monday-Thursday. 28 hrs. Contact: Russell M. Decker, MD, P.O. Box 49412, Los Angeles 90049.

January 24-26—**Pediatric Anesthesiology—13th Clinical Conference.** Children's Hospital of Los Angeles at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $100. Contact: Wayne Herbert, MD, Division of Anesthesiology, Children's Hospital, P.O. Box 54700, L.A. 90054.

January 26-28—**Refresher Course in Urology.** UCI at Center for Health Education, Long Beach. Sunday-Tuesday. Contact: Chuck Paul, UCI, Dept. UNEX, Irvine 92664. (714) 833-5193.

January 26-February 1—**Skiers' Symposium: Pre-, Intra- and Post-Operative Management of the Surgical Patient.** See Of Interest To All, January 26-February 1.

January 29-31—**Advances in Neurology.** UCSF. Wednesday-Friday.

Continuously—**Fellowship in Cleft Palate.** Rancho Los Amigos Hospital, Downey. One-year fellowship in the total evaluation and management of cleft lip and cleft palate patients. Contact: Libby Wilson, MD, Rancho Los Amigos Hosp., 7601 E. Imperial Highway, Downey 90242. (213) 922-7454.

Continuously—**Anesthesia Lecture Series.** UCSD at University Hospital, 3rd floor conference room, San Diego. Wednesdays, 4:45 p.m.

Continuously—**Anesthesiology Mortality and Morbidity Conference.** UCSD at VA Hospital, Rm. 6006, San Diego. Thursdays, 4:30 p.m.

Continuously—**Neurological Sciences.** St. Francis Hospit Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of rad logical evaluations and pathological specimens of curre material and review of current topics in specialty. Week notification of cases available. Contact: Ralph Miller, A min. Asst., St. Francis Hospital, 3630 Imperial Highwa Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Science Lecture Series.** Dept. of Surge St. Mary's Hospital, San Francisco. Mondays, 11:15 a.r 12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgo MD, Dir. of Medical Education, St. Mary's Hospital, 22 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Po graduate traineeships of 4-14 days duration, as you wish. I tuition but donations accepted. Contact: Orthopaedic Di sion, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser S Francisco, and Harkness Memorial Hospitals. Third Tu day of each month, 6:00 p.m. Contact: Charles H. Lithgo MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes S San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at L Angeles County-USC Medical Center. Mondays, 7:00-9: p.m. Contact: Dept. of Orthopedics, USC School of Me 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCS By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arran ment.

Continuously—**Training for Physicians in Nephrology.** CRM Area VI and LLU at LLU. Courses of four weeks or mo available, to be scheduled by arrangement. Hemodialys peritoneal dialysis, renal biopsy, and kidney transplantatio 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, S Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Cla room. Contact: Charles H. Lithgow, MD, Dir. of Med. E St. Mary's Hospital, 2200 Hayes St., San Francisco 9411 (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, S Francisco. Mondays, 1:30 p.m., Morrissey Hall. Conta Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's H pital, 2200 Hayes St., San Francisco 94117. (415) 752-40

Continuously—**Surgical Morbidity and Mortality Conferen** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Ha Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., Mary's Hospital, 2200 Hayes St., San Francisco 94117. (41 752-4000.

Continuously—**Surgical Mortality and Morbidity Conferen** UCSD alternating between University and VA Hospita San Diego. Saturdays. 9:30 a.m.

Continuously—**Ortho Surgical Conference.** UCSD at Univers. Hospital, 3rd floor conference room, San Diego. Wedn days, 8:00 a.m.

Continuously—**Otolaryngology Conference.** UCSD alternati between University and VA Hospitals, San Diego. Frida 8:30 a.m.

Continuously—**Laryngeal Physiology.** UCSD at VA Hospit San Diego. Fridays, 8:30 a.m.

Continuously — **Surgical Pathology Conference.** See Ra ology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin G eral Hospital, Stockton. Fourth Wednesday of each mon 9:00-10:30 a.m., Conference Room 1. Contact: J. D. Kort born, MD, Med. Dir., San Joaquin Gen. Hosp., Stockt 95201. (209) 982-1800.

ontinuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

ontinuously—**Trauma Conference.** UCSD at University Hospital, 1st floor conference room, San Diego. Tuesdays, 3:30 p.m.

ontinuously—**Vascular Surgery Conference.** UCSD alternating between VA and University Hospitals, San Diego. Thursdays, 4:00 p.m.

ontinuously—**Radiology-Urology Conference. Pathology-Urology Conference.** See Radiology and Pathology, Continuously.

ontinuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

and Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Lebanon Hall Auditorium, Cedars-Sinai Hospital, Los Angeles. UCLA.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery.** 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Otolaryngology. 12:00 noon. University and VA Hospitals, San Diego. UCSD.

Neurology, Neuropathology, Neurosurgery. 4:00 p.m. University and VA Hospitals, San Diego. UCSD.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital, 1st, 3rd, 5th Sat.; VA Hospital, 2nd, 4th Sat., San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

Orthopedic Surgery. 8:00-9:00 a.m. UCSF. September 21-June 14, 1975. Subjects to be announced.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

November 17-22—**American Congress of Rehabilitation Medicine.** St. Francis Hotel, San Francisco. Sunday-Friday. Contact: Creston C. Herold, Exec. Dir., ACRM, 30 N. Michigan Ave., Chicago 60602.

November 19—**Association of Academic Physiatrists.** St. Francis Hotel, San Francisco. Tuesday. Contact: George H. Kraft, Sec., Dept. of Rehabilitation Medicine, Univ. of Washington, Seattle 98195.

November 23—**Anesthesia Postgraduate Seminar—Pain, Drug Abuse and Their Management.** See Surgery and Anesthesiology, November 23.

November 29-December 1—**International College of Applied Nutrition—Fall Seminar.** International Hotel, Palm Springs. Friday-Sunday. Contact: Michael Walczak, MD, P.O. Box 386, La Habra 90631. (213) 697-4576.

December 5-6—**Air Pollution Medical Research Conference.** American Medical Association at Sheraton Palace Hotel, San Francisco. Thursday-Friday. Contact: AMA, 535 N. Dearborn St., Chicago, Ill. 60610.

December 7—**Nosocomial Infections.** UCLA. Saturday.

December 7—**Family Practice Symposium.** Southern California Permanente Medical Group at San Diego. Saturday. Contact: Barbara King, Dept. of Research & Education, Rm. 6014, Kaiser-Permanente, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4242.

December 27-28—**Symposium on Innovations in Athletic Conditioning and Sports Medicine—2nd Annual.** University Extension at UC, Berkeley. Friday-Saturday. 15 hrs. $50. Contact: Nathan W. Cohen, PhD, Dir., Curriculum Development in Science, UC Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1061.

January 9-10—**New and Old Antibiotics.** USC. Thursday-Friday.

January 14-April 22—**Acupuncture for Management of Musculo-Skeletal Pain.** UCLA. Mondays, 7-10 p.m.

January 23-24—**Environmental Health and Safety in Health Care Facilties. UCSF.** Thursday-Friday.

January 26-February 1—**Skiers' Symposium: Pre-, Intra- and Post-Operative Management of the Surgical Patient.** Bernard Levinson, MD, Carmichael, Symposium Coordinator. Snowbird-Alta, Utah. Sunday-Saturday. Contact: Daman-Nelson Travel Agency, 115 Mission St., San Francisco. (415) 434-2018.

January 27-31—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 29-February 1—**Physician and the Hospital.** USC at Ahwahnee Hotel, Yosemite. Wednesday-Saturday.

Continuously—**Psychiatric Seminars for Physicians.** San Francisco Psychoanalytic Institute, San Francisco. 1st and 3rd Thursdays, October-May, 1975; 8:00 p.m. Invitations to all non-psychiatric physicians of 9 Bay Area counties. Contact: Jerome D. Oremland, MD, Chr., Extension Division, S. F. Psychoanalytic Institute, 2420 Sutter St., San Francisco 94115. (415) 931-4205.

Continuously—**Emergency Care.** USC. September 17-December 3. Tuesdays, 7:30-10:00 p.m.

Continuously—**Bedside Clinics.** USC. September 26-December 19. Thursdays, 7:30-9:30 p.m.

Continuously—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. October 1-December 3. Tuesdays (except Nov. 5 and 12).

Continuously—**Clinical Conferences.** UCSF at Community Hospital, Santa Cruz. October 9, 1974-June 11, 1975. Wednesdays.

Continuously—**Continuing Medical Education Noon Conferences.** The Hospital of the Good Samaritan, Los Angeles. Every weekday, 12-1 p.m. For monthly calendar, contact: Janie Sternal, Coord., Cont. Med. Ed., Hosp. of the Good Samaritan, 1212 Shatto St., Los Angeles 90029. (213) 482-8111.

Continuously—**Emergency Room Lecture Series.** UCSD at University Hospital, San Diego. Wednesdays, 10:00 a.m.

Continuously—**Endocrinology, Metabolism, Reproductive Medicine, Genetics Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 11:30 a.m.

Continuously—**Preceptorships in International Health, Microbiology, Pharmacology and Experimental Therapeutics, Physiology and Basic Sciences.** UCSF. By special arrangement.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange County Chapter, American Academy of Family Physicians at Saddleback Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; La Palma Intercommunity Hosp., La Palma; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Riviera Hosp., Torrance; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $15 per session. Contact: William J. Newman, MD, 280 Perkins St., Sonoma 95476. (707) 996-2165.

Continuously—**Basic Science Seminar.** UCSD Wednesdays, 9:15 a.m., University Hospital of San Diego County, San Diego. Contact: UCSD.

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MEDICAL GRAND ROUNDS

Providence Hospital, Providence Hall Auditorium, 700 N 47th Avenue, Portland 97213:

November 6—7:00 p.m.—**Comprehensive Health Plann What are the Goals?**

November 12—7:00 p.m.—**Ampicillin: Reassessment A 20 Years**

November 20—8:00 a.m.—**Clinicopathologic Conference**

December 11—7:00 p.m.—**Blue Cross as a Consumer Ac cate**

December 17—7:00 p.m.—**Newer Approaches to the Tr ment of Leukemia**

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November 30-December 4—**American Medical Associa Clinical Meeting,** Portland. Contact: Ernest B. Howard, M AMA, 535 N. Dearborn Avenue, Chicago, IL 60610.

November 30—**16th Conference of Medical Aspects of Sp** Memorial Coliseum, Portland. Contact: AMA Committee Medical Aspects of Sports, 535 N. Dearborn Avenue, C cago, IL 60610.

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In order to have future activities listed here or to rec information on these and other activities, please write Joan M. Kelday, Information Specialist, Continuing Med Education, WAMI Program, University of Washington Sch of Medicine, E-301, Health Sciences Building, SC Seattle, Washington 98195. Phone: (206) 543-6995.

November 14-15—**Drug Therapy.** Thursday-Friday, Seattle hrs. $50. Contact: Mr. Richard L. Reimer, Asst. Dir. C E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Se 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

nkers Equity Development
Sutter Place Medical Center 42

ehringer Ingelheim Ltd.
Catapres 7, 8, 9, 10, 11, 12, 46, 47

ion Laboratories Inc.
Bronkotabs ..... 4th Cover

ssified 26, 27

A—104th Annual Session and Western entific Assembly
Hotel Accommodations 38

npton Foundation 26

ry Council of California 5

rsey Laboratories
Triaminic Syrup 6
Triaminic Expectorant Plain 25

ac Inc.
Neoject 3

eside Laboratories
Norpramin 36, 37

Eli Lilly and Company, Inc.
Manufacturer of Darvon Compound-65 and Darvocet-N 100 28

Loma Linda Foods
Soyalac 13

Merck Sharp & Dohme
Aldomet 20, 21, 22
Triavil 32, 33, 34

Obetrol Pharmaceuticals
Obetrol 24

Pharmaceutical Manufacturers Association
Prescription Ads 30, 31

Presto Food Products Inc.
Mocha Mix 35

PVO International Inc.
Saffola 29

A. H. Robins Company
Donnagel-PG/Robitussin 17, 18, 19

Roche Laboratories
Valium ..... 2nd Cover and Page 1

Roerig (Pfizer)
Emete-Con 14, 15

G. D. Searle & Co.
Lomotil ..... 56 and 3rd Cover

Security Pacific Bank 16, 39

Smith, Kline & French Laboratories
Ornade 4

State Compensation Insurance Fund 23

University of California, San Francisco
Extended Medical Education—Neurology .. 49

University of Southern California School of Dentistry
Continuing Education 51

Warner-Chilcott Laboratories
Proloid 44, 45

Wyeth Laboratories
Bicillin/Wycillin 40, 41

---

ovember 15-16—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. No fee. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext 470.

ovember 21-22—**Care of the Critically Ill Patient.** Thursday-Friday. Olympic Hotel and Harborview Medical Center, Seattle. $45 for physicians, $30 for nurses and other health professionals. Contact: Mr. Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

cember 5-6—**Hypertension.** Thursday-Friday. Seattle. 12 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, 98195. (206) 543-1050.

uary 16-17—**What's New in Pediatrics '75.** Thursday-Friday. Seattle. Fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, 98195. (206) 543-1050.

uary 22-24—**Advances in Neurology.** Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 18 hrs. $100, ACP members; $150, non-members; $50, ACP Associates. Contact: M. H. Jackson, Registrar, Postgraduate Courses, American College of Physicians, 4200 Pine St., Philadelphia, Pa., 19104.

uary 24-25—**Tax, Estate and Financial Planning for Physicians.** Friday-Saturday. Seattle. Fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

uary 26-February 1—**Advances in Perinatology.** Sunday-Saturday. Sun Valley, Idaho. 37½ hrs. $100 for physicians, $30 for nurses and other health professionals. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

ruary 7-8—**A Modern Approach to Allergy.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

ruary 19-20—University of Washington School of Medicine's Western Circuit Course: **Trauma-Burns-Shock, Emergency Medical Care.** Longview Wash., Feb. 19; Olympia, Wash., Feb. 20. 4 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 20-21—**Thirteenth Annual Symposium on Respiratory Disease.** Thursday-Friday. Olympic Hotel, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 28-March 1—**The Intensive Care Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

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1. Location of known office of publication: 731 Market Street, San Francisco, California 94103.

2. Location of the headquarters or general business office of the publisher: 731 Market Street, San Francisco, California, 94103.

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1. Demeulenaere, L.: Action du R 1132 sur le transit gastro-intestinal, Acta Gastroent. Belg. 21:674-680 (Sept.-Oct.) 1958.

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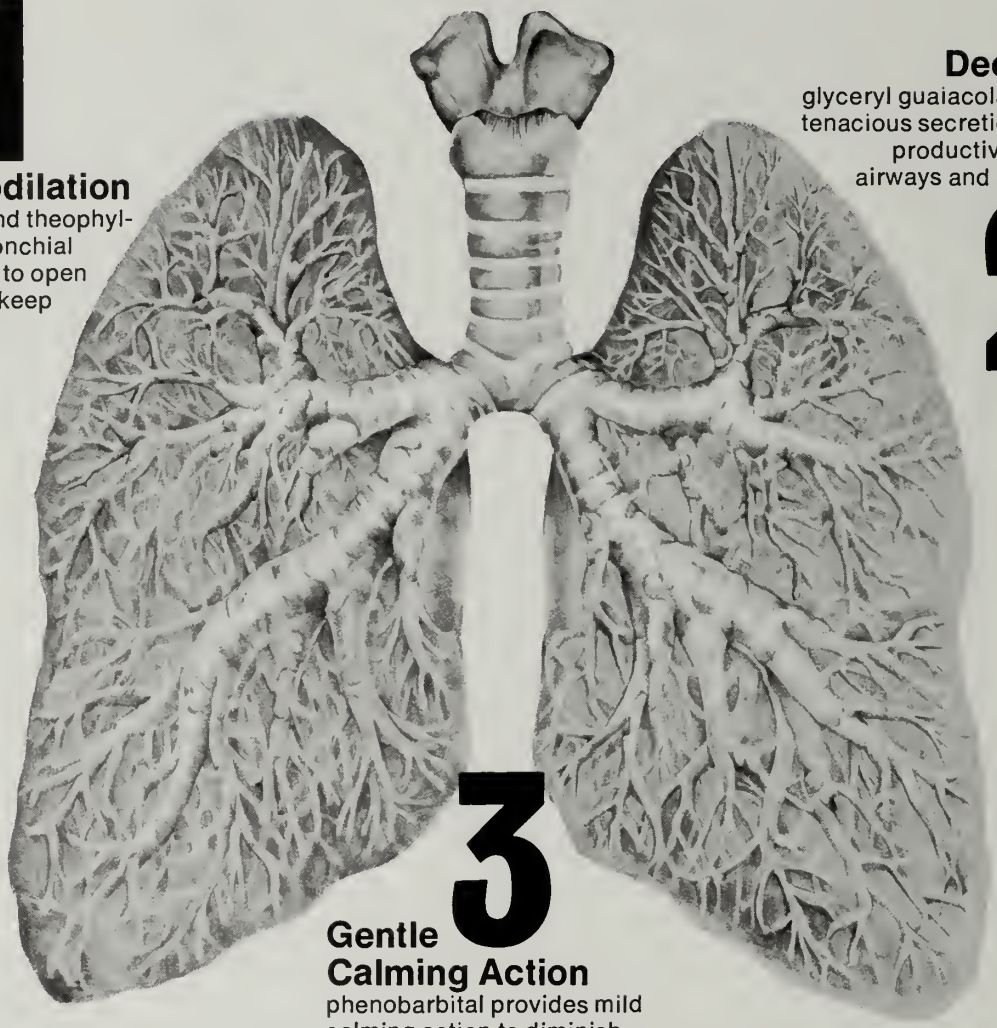

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VOLUME 121 • NUMBER 6 **DECEMBER 1974**

449 *Nonocclusive Hemorrhagic Necrosis of the Intestine*
SHELDON E. COHEN, MD, MARTIN I. FELDMAN, MD, and EARL F. WOLFMAN, JR., MD

456 *Seminars in Infectious Disease: A New Look at Infectious Gastroenteritis*
JOSEPH W. ST. GEME, JR., MD

MEDICAL PROGRESS
462 *Pseudomembranous Enterocolitis—Resurgence Related to Newer Antibiotic Therapy*
EMMET B. KEEFFE, MD, RONALD M. KATON, MD, TSOI T. CHAN, MD, CLIFFORD S. MELNYK, MD, and JOHN A. BENSON, JR., MD

SPECIALTY CONFERENCE
473 *The Sick Sinus and Ailing Atrium*
Participants: MELVIN M. SCHEINMAN, MD, ROBERT PETERS, MD, DAVID S. HIRSCHFELD, MD, JOSEPH A. ABBOTT, MD, and FRED KUNKEL, MD
University of California, San Francisco, and San Francisco General Hospital

MEDICAL STAFF CONFERENCE
482 *Dissecting Aneurysm* Discussion by JOHN R. STONER, MD

490 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Plastic Surgery*

495 EDITORIALS • *On Training Health Manpower for Primary Care* • *Sicknesses of the Sinus Node* • *The Clergy and Patient Care* • *Pseudomembranous Colitis*

CASE REPORTS
501 *Shigella Dysenteriae Type 1—Severe Dysentery and Sepsis with Hematologic, Hepatic and Renal Complications* VICTOR D. LEVINE, MD, GARY D. OVERTURF, MD, and ALLEN W. MATHIES, MD, PhD

504 *Clindamycin Colitis—An Emerging Problem* WILLIAM D. CAREY, MD, and MARTIN BROTMAN, MD

508 LETTERS TO THE EDITOR

TRAUMA ROUNDS
510 *Penetrating Thoracic Trauma* Chief Discussant: ARTHUR N. THOMAS, MD

MEDICAL EDUCATION
514 *A Developing Regional Network Residency Program in Family Practice*
JOHN P. GEYMAN, MD, and THOMAS C. BROWN, PhD

SPECIAL ARTICLE
521 *What Is So Special About a Family Physician?* JOSEPH B. DEISHER, MD

532 *In Memoriam*

534 *Volume Index*

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(See Advertising Page 22)

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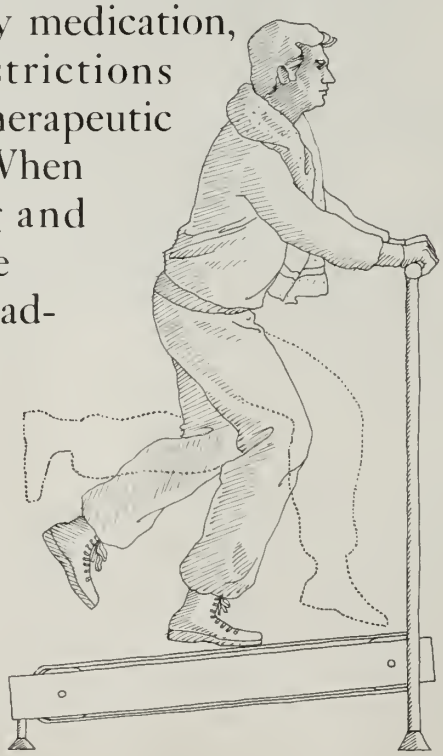

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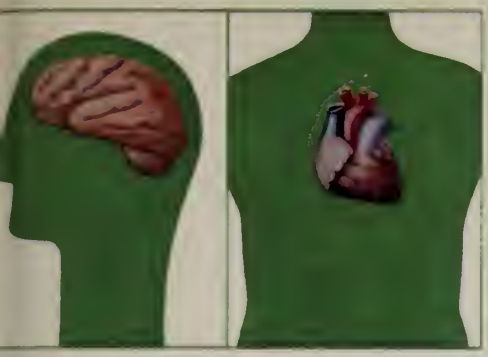

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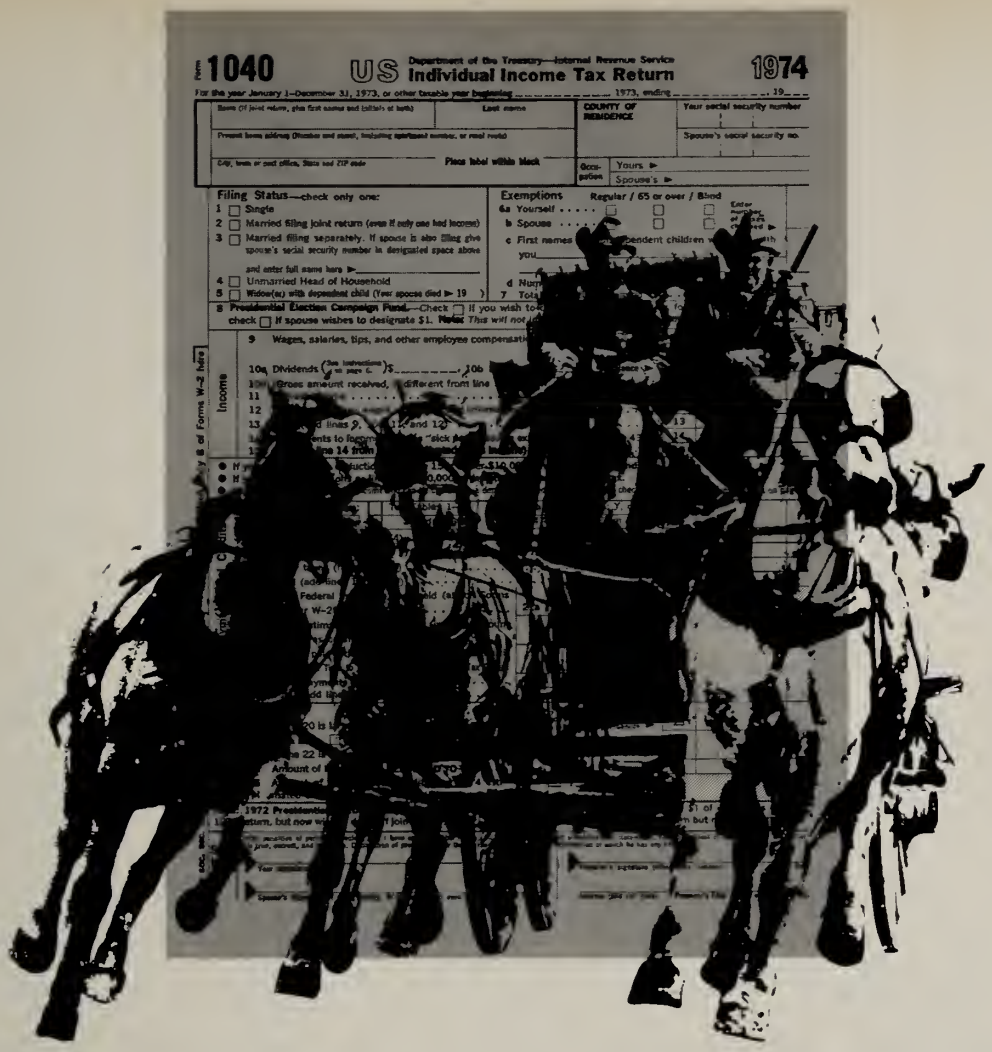

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Bio-Science Reports

TSH by RIA at BSL

Bio-Science Laboratories adds still another valuable boratory aid for the diagnosis of thyroid disorders: serum hyroid Stimulating Hormone (TSH) by radioimmunoassay IA). The exquisite sensitivity of the RIA technic permits e detection of normal levels of TSH, which have been ported to average about 4.0 microunits/ml with a range "non-detectable to 10 microunits/ml" (Hershman, J. M. d Pittman, J. A., New Eng. J. Med. *285*:997, 1971).

The RIA method for TSH was pioneered by Utiger and dell *et al.* in 1965. We are employing Hershman's modifiation of this method. Hershman and Pittman have reviewed e utility of the RIA of serum TSH in man (Annals Intern. ed. *74*:481, 1971) and have emphasized its usefulness th for establishing the diagnosis of primary hypothyroidm and for differentiating it from hypothyroidism secondary hypopituitarism. TSH levels above normal are strongly ggestive of the existence of primary hypothyroidism and ay in fact be the most sensitive index of this disease.

Quotable Quotes

OLATE:

". . . the results support the suggestion that red cell folate ovides a better assessment of folate status than does rum folate." (J. Clin. Path. *22*:212, 1969).

". . . serum folate assay is a valuable routine test in paents who have a macrocytic anaemia and low serum tamin B_{12}." (J. Clin. Path. *24*:244, 1971).

ote: We offer both serum and red cell folate measureents. As a matter of fact, if you order a red cell folate, r report includes both serum and red cell values.

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"HAI (hemagglutination inhibition) antibodies are the first be detectable, around 12-15 days after exposure; they se rapidly and reach peak titers within one to three weeks . . . , and the CF response is delayed 10-14 days after nset, with maximal titers being attained after three or four eeks." (J. Infect. Diseases *123*:640, 1971).

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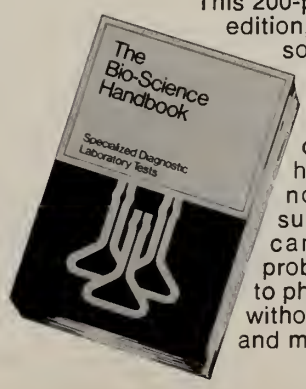


This 200-page book, now in its tenth edition, is a uniquely informative source to keep you up-to-date on the newer laboratory tests, such as serum TSH, available to clinicians. You will find it a handy reference guide for normal values and quick summations on tests which can aid in your diagnostic problems. Copies are available to physicians and lab personnel without obligation. Simply fill out and mail this coupon.

The Role of the Detail Man

Opinion & Dialogue

Dr. Willard Gobbell
Family Physician
Encino, California

"I may be prejudiced, but I ai very much in favor of the detail me I meet. Most of them are knowledg able about the drugs they promote and can be a great help in acquain ing me with new medication."

Family Physician's Perception

I think that most general practitioners in this area feel as I do about the detail man. Over the years I have gotten to know most o the men who visit me regularly anc they in turn have become aware of my particular interests and the na ture of my practice. They, there fore, limit their discussion as muc as possible to the areas of interest to me. Since I usually see the same representative again in future visits, it is in his best interest to supply me with the most honest, factual, as well as up-to-date information about his products.

Dr. Jeremiah Stamler
Chairman
Department of Community Health and Preventive Medicine, and Dingman Professor of Cardiology
Northwestern University Medical School

"In the total picture of dealin with health problems in this count there is a potential for detail men to play a meaningful role."

The Positive Influence

My contact with representa tives and salesmen of the pharma ceutical industry is the type of con tact that people in a medical cente research people, and academic people have and that's in all likelih on a somewhat different level from that of the practicing physician.

Let me touch on how I person ally perceive the role of the sales representative. These men reach large numbers of health profes sionals. Thus they could be—and at times actually are—disseminators of useful information. They could consistently serve a real edu cational function in their ability to discuss their products.

At present they do distribute printed material, brochures and pamphlets—some of it scientific ally sound and therefore truly use ful—as well as some excellent film produced by the pharmaceutical industry. When they function in th

Ie a Source of Information?

Yes, with certain reservations. e average sales representative s a great fund of information out the drug products he is re- onsible for. He is usually able to swer most questions fully and elligently. He can also supply rints of articles that contain a at deal of information. Here, , I exercise some caution. I usu- accept most of the statements d opinions that I find in the pers and studies which come m the larger teaching facilities. oes without saying that a physi- n should also rely on other rces for his information on armacology.

ining of Sales Representatives

Ideally, a candidate for the sition as a sales representative a pharmaceutical company ould be a graduate pharmacist o has a questioning mind. I don't nk this is possible in every case, d so it becomes the responsibility of the pharmaceutical company to train these individuals comprehensively. It is of very great importance that the detail man's knowledge of the product he represents be constantly reviewed as well as updated. This phase of the sales representative's education should be a major responsibility of the medical department of the pharmaceutical company.

I am certain that most of these companies take special care to give their detail men a great deal of information about the products they produce—information about indications, contraindications, side effects and precautions. Yet, although most of the detail men are well informed, some, unfortunately, are not. It might be helpful if sales representatives were reassessed every few years to determine whether or not they are able to fulfill their important function. Incidentally, I feel the same way about periodic assessments of everyone in the health care field, whether they be general practitioners, surgeons or salesmen.

Value of Sampling

I personally am in favor of limited sampling. I do not use sampling in order to perform clinical testing of a drug. I feel that drug testing should rightly be left to the pharmacology researcher and to the large teaching institutions where such testing can be done in a controlled environment.

I do not use samples as a "starter dose" for my patients. I do, however, find samples of drugs to be of value in that they permit me to see what the particular medication looks like. I get to see the various forms of the particular medication at first hand, and if it is in a liquid form I take the time to taste it. In that way I am able to give my patients more complete information about the particular medications that I prescribe for them.

---

pacity they are indeed useful; ticularly in the fact that they seminate broadly based educa- nal material and serve not just 'pushers" of their drugs.

: Other Side of the Coin

Obviously, the pharmaceuti- companies are not producing all s material as a labor of love— y are in the business of selling ducts for profit. In this regard ambitious and improperly moti- ed sales representative can rt a negative influence on the cticing physician, both by pre- ting a one-sided picture of his duct, and by encouraging the ctitioner to depend too heavily drugs for his total therapy. In se ways, the salesman has often torted objective reality and dermined his potential role as an ucator.

: Industry Responsibility

Since the detail man must be information resource as well as epresentative of his particular armaceutical company, he ould be carefully selected and thoroughly trained. That training, perforce, must be an ongoing one. There must be a continuing battle within and with the pharmaceutical industry for high quality not only in the selection and training of its sales representatives, but also in the development of all of its promotional and educational material.

The industry must be ready to accept constructive as well as corrective criticism from experts in the field and consumer spokesmen, and be willing to accept independent peer review. The better educated and prepared the salesman is, the more medically accurate his materials, the better off the pharmaceutical industry, health professionals and the public—*i.e.*, the patients—will be.

Physician Responsibility

The practicing physician is in constant need of up-dated information on therapeutics, including drugs. He should and does make use of drug information and answers to specific questions supplied by the pharmaceutical representative. However, that information must not be his main source of continuing education. The practitioner must keep up with what is current by making use of scientific journals, refresher courses, and information received at scientific meetings.

The practicing physician not only has the right, but has the responsibility to demand that the pharmaceutical company and its representatives supply a high level of valid and useful information. I feel certain that if such a high level is demanded by the physician as well as the public, this demand will be met by an alert and concerned pharmaceutical industry.

From my experience, my impression is that sectors of the pharmaceutical industry are indeed ethical. I challenge the industry as a whole to live up to that word in its finest sense.

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

P·M·A

IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparati should not be used. Antihistaminics appear beneficial in tre ment of procaine reaction.

The use of antibiotics may result in overgrowth of nons ceptible organisms. Constant observation of the patient is ess tial. If new infections due to bacteria or fungi appear dur therapy, discontinue penicillin and take appropriate measure

If allergic reaction occurs, withdraw penicillin unless, in opinion of the physician, the condition being treated is threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected prim or secondary syphilis, perform proper diagnostic procedur including darkfield examinations. In all cases in which conco tant syphilis is suspected, perform monthly serological tests for least four months.

Adverse Reactions: (Penicillin has significant index of s sitization) skin rashes, ranging from maculopapular eruptions exfoliative dermatitis; urticaria; serum sickness-like reactio including chills, fever, edema, arthralgia and prostration. Sev and often fatal anaphylaxis has been reported. (See "Warnings"

As with other antisyphilitics, Jarisch-Herxheimer reaction been reported.

Administration and Dosage: Administer only by *deep in muscular injection,* in upper outer quadrant of buttock. In infa and small children, midlateral aspect of thigh may be preferat When doses are repeated, vary injection site. Before injecti aspirate to be sure needle bevel is not in blood vessel. If blo appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have creased susceptibility to penicillin, this resistance is relative, absolute, and penicillin in large doses remains the drug of choi Physicians are cautioned not to use less than recommenc doses.

Gonorrheal infections (uncomplicated)—Men or Women: million units intramuscularly divided into at least two doses a injected at different sites at one visit, together with 1 gram of c probenecid, preferably given at least 30 minutes prior to injectic

NOTE: Treatment of severe complications of gonorrhea shou be individualized using large amounts of short-acting penicil Gonorrheal endocarditis should be treated intensively w aqueous penicillin G. Prophylactic or epidemiologic treatment gonorrhea (male and female) is accomplished with same tre ment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Ve real Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after thera In the male, a gram-stained smear is adequate if positive; oth wise, a culture specimen should be obtained from the anter urethra. In the female, culture specimens should be obtain from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persi 3 or more days following initial therapy and smear or cultu remains positive. Follow-up treatment consists of 4.8 million un I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment indicated if follow-up cervical or rectal cultures remain positive *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million ur daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test syphilis at the time of diagnosis. Patients with gonorrhea w also have syphilis should be given additional treatment app priate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,0 units (4-cc. size) contains procaine penicillin G in a stabiliz aqueous suspension with sodium citrate buffer, and as w/v appro imately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% po vinylpyrrolidone, 0.01% propylparaben and 0.09% methylparabe The multiple-dose 10-cc. vial contains per cc. 300,000 units p caine penicillin G in a stabilized aqueous suspension with sodi citrate buffer and approximately 7 mg. lecithin, 2 mg. carbo methylcellulose, 3 mg. polyvinylpyrrolidone, 0.5 mg. sorbit monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmita 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS

INJECTION

Bicillin® LONG-ACTING

STERILE BENZATHINE PENICILLIN G (SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

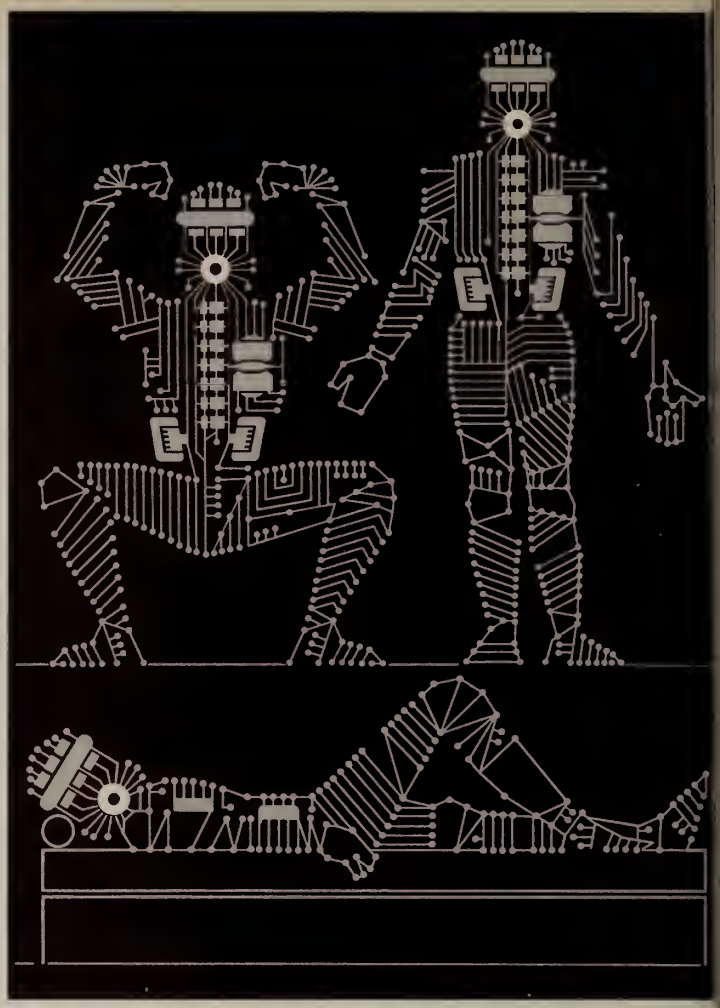
Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

S. Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

Catapres Man. He doesn't have to take it lying down.

Orthostatic effects are mild and infrequent; normal hemodynamic responses to exercise are not altered



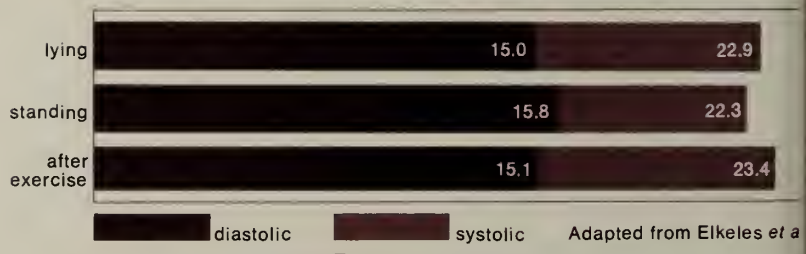
Catapres reduces blood pressure to virtually the same exter in both the lying and standing positions and after exercise (see chart).

Postural hypotension is therefore rarely a problem. And normal hemodynamic responses to exercise remain essentially unchanged.

Catapres. A new antihypertensive agent whose mechanisn of action appears to be central alpha-adrenergic stimulation as demonstrated in animal studies.

Try Catapres. Because *how* you lower blood pressure can make a difference.

Mean blood pressure reduction (mm Hg) after 4 weeks in 9 hypertensive patients receiving Catapres (0.15 mg/day)



Adapted from Elkeles *et a*

new Catapres®
(clonidine hydrochloride)

Tablets of 0.1 and 0.2 mg

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Elmsford, New York 10523

Please see adjoining colum for brief summary of prescribing information.

ew **Catapres®**
clonidine hydrochloride)

olets of 0.1 mg and 0.2 mg
dication: The drug is indicated in the treatment of hyperten-
n. As an antihypertensive drug, Catapres (clonidine hydro-
oride) is mild to moderate in potency. It may be employed in
eneral treatment program with a diuretic and/or other antihy-
tensive agents as needed for proper patient response.
rnings: Tolerance may develop in some patients necessitating
eevaluation of therapy.
age in Pregnancy: In view of embryotoxic findings in animals,
d since information on possible adverse effects in pregnant
men is limited to uncontrolled clinical data, the drug is not
ommended in women who are or may become pregnant unless
potential benefits outweigh the potential risk to mother
d fetus.
age in Children: No clinical experience is available with the
of Catapres (clonidine hydrochloride) in children.
cautions: When discontinuing Catapres (clonidine hydro-
oride), reduce the dose gradually over 2 to 4 days to avoid
ossible rapid rise in blood pressure and associated sub-
tive symptoms such as nervousness, agitation, and headache.
ients should be instructed not to discontinue therapy with-
consulting their physician. Rare instances of hypertensive
cephalopathy and death have been recorded after cessation of
nidine hydrochloride therapy. A causal relationship has not
en established in these cases. It has been demonstrated that
excessive rise in blood pressure, should it occur, can be
ersed by resumption of clonidine hydrochloride therapy or
intravenous phentolamine. Patients who engage in potentially
zardous activities, such as operating machinery or driving,
uld be advised of the sedative effect. This drug may enhance
CNS-depressive effects of alcohol, barbiturates and other
datives. Like any other agent lowering blood pressure, cloni-
e hydrochloride should be used with caution in patients with
ere coronary insufficiency, recent myocardial infarction,
ebrovascular disease or chronic renal failure.
s an integral part of their overall long-term care, patients
ated with Catapres (clonidine hydrochloride) should receive
iodic eye examinations. While, except for some dryness of
eyes, no drug-related abnormal ophthalmologic findings have
en recorded with Catapres, in several studies the drug pro-
ced a dose-dependent increase in the incidence and severity
spontaneously occurring retinal degeneration in albino rats
ated for 6 months or longer.
verse Reactions: The most common reactions are dry mouth,
wsiness and sedation. Constipation, dizziness, headache, and
gue have been reported. Generally these effects tend to
inish with continued therapy. The following reactions have
en associated with the drug, some of them rarely. (In some
tances an exact causal relationship has not been established.)
ese include: Anorexia, malaise, nausea, vomiting, parotid pain,
d transient abnormalities in liver function tests; one report of
sible drug-induced hepatitis without icterus and hyperbili-
inemia in a patient receiving clonidine hydrochloride, chlor-
lidone and papaverine hydrochloride.
Veight gain, transient elevation of blood glucose, or serum
atine phosphokinase; congestive heart failure, Raynaud's
enomenon; vivid dreams or nightmares, insomnia, other be-
vioral changes, nervousness, restlessness, anxiety and mental
pression. Also rash, angioneurotic edema, hives, urticaria,
nning of the hair, pruritus not associated with a rash, impo-
ce, urinary retention, increased sensitivity to alcohol, dryness,
ning or burning of the eyes, dryness of the nasal mucosa, pallor,
recomastia, weakly positive Coombs' test, asymptomatic elec-
cardiographic abnormalities manifested as Wenckebach period
ventricular trigeminy.
erdosage: Profound hypotension, weakness, somnolence, di-
nished or absent reflexes and vomiting followed the accidental
estion of Catapres (clonidine hydrochloride) by several chil-
n from 19 months to 5 years of age. Gastric lavage and ad-
nistration of an analeptic and vasopressor led to complete
overy within 24 hours. Tolazoline in intravenous doses of
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erence: 1. Elkeles, R. S., Goldby, F. S. and Oliver, D. O.:
ouble Blind Study of Catapres, A New Hypotensive Agent,
Conolly, M. E. (ed.): Catapres in Hypertension, London,
terworths, 1970, pp. 139-144.

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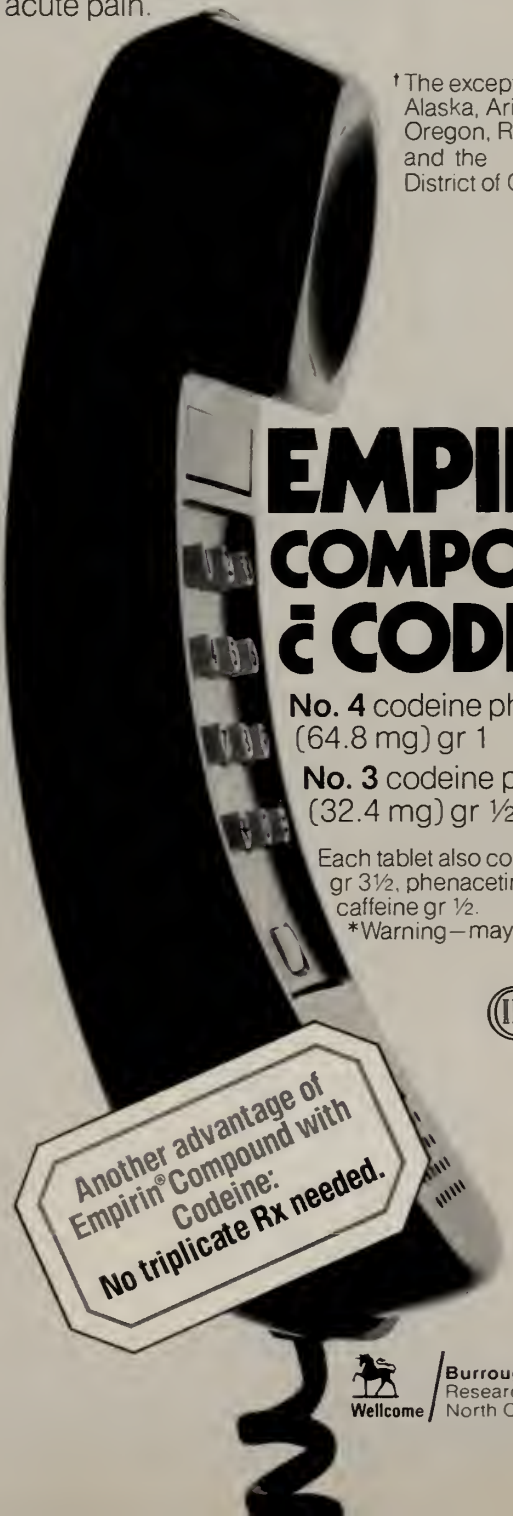

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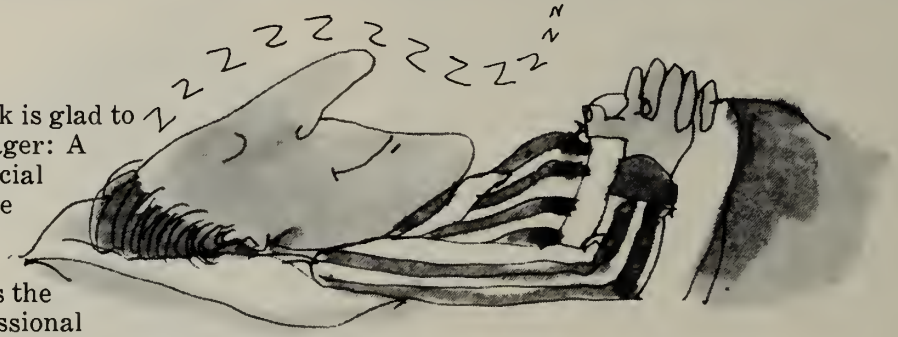

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obvious moderate to severe anxiety
with a less obvious underlying depression

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a tranquilizer-antidepressant

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"All right, I agree, she was obviously very anxious...you said she hadn't been sleeping..."

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"...that's a good place to s t Did you find anything wrc with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

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Not a thing... negative... nothing organically wrong. Still has a fair list of somatic complaints. I've tried to reassure her... to let her talk... to help her sort things out. She's been in to see me a number of times."

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"Just what I was coming to... I've had her on tranquilizers. And *that's* what puzzles me. I'm not getting the response I hoped for. She's no better... perhaps a little worse. It's sad to see."

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WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. In patients with angle-closure glaucoma, even average doses may precipitate an attack. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either cons uent alone.

Perphenazine: Side effects may be any of those reported wi phenothiazine drugs: extrapyramidal symptoms (opisthotonus, oc logyric crisis, hyperreflexia, dystonia, akathisia, acute dyskines ataxia, parkinsonism) can usually be controlled by the concomita use of effective antiparkinsonian drugs and/or by reduction in dc age, but sometimes persist after discontinuation of the phenothiazin

Tardive dyskinesia may appear in some patients on long-term th apy or may occur after drug therapy with phenothiazines and relate agents has been discontinued. The risk appears to be greater elderly patients on high-dose therapy, especially females. Sympton are persistent and in some patients appear to be irreversible. Tl syndrome is characterized by rhythmical involuntary movements the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing cheeks, puckering of mouth, chewing movements). Involuntary mov ments of the extremities sometimes occur. There is no known tre ment for tardive dyskinesia; antiparkinsonism agents usually do n alleviate the symptoms. It is advised that all antipsychotic agents b discontinued if the above symptoms appear. If treatment is reinsti ted, or dosage of the particular drug increased, or another drug su stituted, the syndrome may be masked. It has been suggested th fine vermicular movements of the tongue may be an early sign of tl syndrome, and that the full-blown syndrome may not develop if me cation is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itchir erythema, urticaria, eczema, up to exfoliative dermatitis); oth allergic reactions (asthma, laryngeal edema, angioneurotic eden anaphylactoid reactions); peripheral edema; reversed epinephri effect; hyperglycemia; endocrine disturbances (lactation, gala torrhea, gynecomastia, disturbances of menstrual cycle); altere cerebrospinal fluid proteins; paradoxical excitement; hypertensic hypotension, tachycardia, and ECG abnormalities (quinidine-li effect); reactivation of psychotic processes; catatonic-like state autonomic reactions, such as dry mouth or salivation, headac anorexia, nausea, vomiting, constipation, obstipation, urina frequency or incontinence, blurred vision, nasal congestion, and change in pulse rate; hypnotic effects; pigmentary retinopathy; c neal and lenticular pigmentation; occasional lassitude, muscle we ness, mild insomnia. Other adverse reactions reported with vario phenothiazine compounds include blood dyscrasias (pancytoper thrombocytopenic purpura, leukopenia, agranulocytosis, eosinop ia); liver damage (jaundice, biliary stasis); grand mal convulsior cerebral edema; polyphagia; photophobia; skin pigmentation; a failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported this drug, but which have occurred with other pharmacologically si lar tricyclic antidepressant drugs. *Cardiovascular:* Hypotensic hypertension; tachycardia; palpitation; myocardial infarction; arrhy mias; heart block; stroke. *CNS and Neuromuscular:* Confusior states; disturbed concentration; disorientation; delusions; hallucii tions; excitement; anxiety; restlessness; insomnia; nightmares; nun ness, tingling, and paresthesias of the extremities; periphe neuropathy; incoordination; ataxia; tremors; seizures; alteration EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinerg* Dry mouth; blurred vision; disturbance of accommodation; consti tion; paralytic ileus; urinary retention; dilatation of urinary tra *Allergic:* Skin rash; urticaria; photosensitization; edema of face a tongue. *Hematologic:* Bone marrow depression including agran cytosis; leukopenia; eosinophilia; purpura; thrombocytopenia. G *trointestinal:* Nausea; epigastic distress; vomiting; anorex stomatitis; peculiar taste; diarrhea; parotid swelling; black tong *Endocrine:* Testicular swelling and gynecomastia in the male; bre enlargement and galactorrhea in the female; increased or decreas libido; elevated or lowered blood sugar levels. *Other:* Dizzine weakness; fatigue; headache; weight gain or loss; increased pers ration; urinary frequency; mydriasis; drowsiness; jaundice; alope *Withdrawal Symptoms:* Abrupt cessation after prolonged adminis tion may produce nausea, headache, and malaise. These are indicative of addiction.

OVERDOSAGE: All patients suspected of having taken an ov dosage should be admitted to a hospital as soon as possible. Tre ment is symptomatic and supportive. However, the intravenc administration of 1-3 mg of physostigmine salicylate has be reported to reverse the symptoms of tricyclic antidepressant pois ing. On this basis, in severe overdosage with perphenazine-a triptyline combinations, symptomatic treatment of cent anticholinergic effects with physostigmine salicylate should considered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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Refer to: Cohen SE, Feldman MI, Wolfman EF Jr: Nonocclusive hemorrhagic necrosis of the intestine. West J Med 121: 449-455, Dec 1974

Nonocclusive Hemorrhagic Necrosis of the Intestine

SHELDON E. COHEN, MD, MARTIN I. FELDMAN, MD, *and* EARL F. WOLFMAN, JR., MD
Davis, California

Hemorrhagic intestinal necrosis occurs without demonstrable mechanical obstruction of the mesenteric vascular supply. The etiologic factors include (1) congestive heart failure, (2) cardiac arrhythmia, (3) dehydration, and (4) digitalis therapy with or without digitalis toxicity. All of these factors have been shown to result in a decrease in splanchnic blood flow. The outcome of this disease has invariably been fatal. Early recognition and nonoperative management directed toward increasing splanchnic blood flow are the most significant factors in the survival of patients.

APPROXIMATELY 20 PERCENT of the cases of hemorrhagic intestinal necrosis occur without demonstrable obstruction of the mesenteric arterial or venous blood supply. The occurrence of this condition was first documented in the American literature in 1943 by Thorek.[12] It has been suggested on numerous occasions that nonocclusive hemorrhagic necrosis of the intestine is directly related to congestive heart failure,[1-13] digitalis therapy, and digitalis toxicity.[14-18] Although the clinical and pathologic manifestations are distinctive, the entity remains relatively unknown and the diagnosis is infrequently made, even after diagnostic celiotomy. As a result, the outcome of this disease has invariably been fatal. In this report, a review of the literature is presented, discussing the possible etiologic factors as well as the clinical and pathologic features. The case of a patient with nonocclusive hemorrhagic intestinal necrosis thought to be secondary to digitalis intoxication is also presented as the only known survivor of this condition. Guidelines to the diagnosis and treatment are outlined.

From the Department of Surgery, University of California, Davis, School of Medicine.

Submitted April 16, 1974.

Reprint requests to: S. E. Cohen, MD, Department of Surgery, University of California, Davis, School of Medicine, Davis, CA 95616.

Report of a Case

A 59-year-old Caucasian woman was admitted to the University of California, Davis, Sacramento Medical Center on March 20, with complaint of severe abdominal pain. Four days before admission she deliberately ingested 30 tablets (3 grams) of digitalis leaf. She had been taking 100 mg digitalis leaf daily, a thiazide diuretic (Naturetin®), 5 mg daily, and potassium chloride supplement for several years because of congestive heart failure. There was no recent history of dyspnea, orthopnea, chest pain, palpitation, or edema. Approximately 25 hours after the overdose, nausea and vomiting occurred. Abdominal pain was not present until the morning of admission, when severe intermittent abdominal cramps were noted.

On physical examination the patient was observed to be dehydrated, alert, agitated, and

acutely ill. Blood pressure was 170/90 mm of mercury, the pulse 100 per minute and irregular, and the temperature 37.2°C (99°F). Neck veins were not distended. No rales or ronchi were noted on auscultation of the lungs. A holosystolic murmur was heard loudest at the cardiac apex with radiation to the left sternal border and left axilla. The abdomen was soft and not distended, but there was moderate diffuse tenderness and voluntary guarding on palpation. No masses or visceromegaly were noted. Bowel sounds were absent. The rectal ampulla contained 4+ hematest-positive stool. The extremities were cool without cyanosis or edema. Peripheral pulses were palpable. There were no petechiae or ecchymoses and the remainder of the physical examination was within normal limits.

Laboratory data on admission were: hematocrit 56 percent, hemoglobin 19.2 grams per 100 ml, leukocytes 29,300 per cu mm with a pronounced shift to the left. The serum electrolytes were: sodium 110, potassium 6.7 and chloride 78 mEq per liter. Blood urea nitrogen was 60 mg per 100 ml and creatinine was within normal limits, as was serum amylase. Results of urinalysis were normal. The platelet count was 35,000 per cu mm and the fibrinogen screen was 250 to 300 mg per 100 ml. Partial thromboplastin time, prothrombin time and thrombin time were all normal. Roentgenograms of the chest showed no acute pulmonary disease and the cardiac silhouette was normal. Radiographic films of the abdomen in the supine and erect positions demonstrated normal intestinal gas pattern with no signs of ileus. An electrocardiogram showed a high degree of atrioventricular block with periods of 2:1 block and atrioventricular dissociation. The intraventricular conduction defect along with diffuse ST segment depression was compatible with digitalis toxicity.

During the three hours following admission, the abdominal pain continued to be severe, generalized, and intermittent. A nasogastric tube was placed and 500 ml of "coffee ground" fluid was aspirated. A diagnosis of mesenteric thrombosis was subsequently made, and, after appropriate preoperative preparation, diagnostic celiotomy was carried out.

Exploration of the abdomen showed the small intestine, from the ligament of Treitz to the ileocecal valve, thickened and violaceous in some segments, while normal in others. No peristalsis was evident. In none of the involved segments did the bowel appear to be gangrenous. The mesenteric arterial system was pulsating throughout, with no demonstrable occlusion. The mesenteric venous system also appeared to be patent and without engorgement. Frozen section histologic examination of a wedge biopsy specimen of the jejunum taken from a decidedly discolored area showed necrosis of the mucosa, engorgement of the submucosal vessels and a normal muscularis and serosa (Figure 1). The pathologic diagnosis was hemorrhagic enteropathy of the small bowel. Massive resection of the small bowel was decided against, and the abdomen was closed.

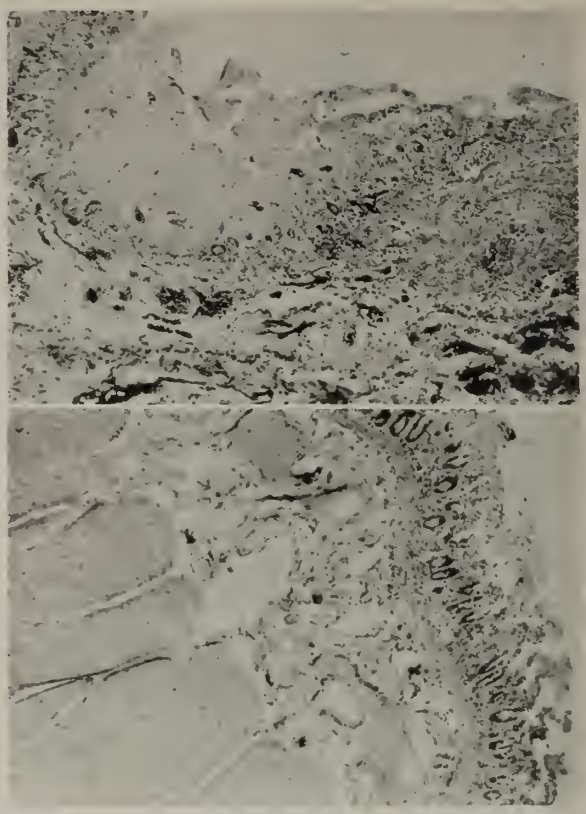

Figure 1.—Section of diseased small bowel demonstrating (in top frame) distortion of the mucosal architecture, engorgement of the mucosal and submucosal veins and (in lower frame) little or no involvement of the muscularis.

Postoperatively, penicillin and kanamycin were administered. Heparin and low molecular weight dextran were also given to prevent thrombosis of mesenteric vessels. Sixteen liters of intravenous fluid including colloid were required during the first 48 hours to maintain the vital signs within normal limits and an adequate urinary output.

On the third postoperative day significant respiratory distress developed. Roentgenograms of the chest showed a collapsed right upper lobe and

Figure 2.—Upper gastrointestinal x-ray study on the eighteenth postoperative day. The distal small bowel shows changes consistent with submucosal edema or hemorrhage.

Figure 3.—An upper gastrointestinal study on thirty-fifth postoperative day showed complete resolution of earlier changes.

diffuse bilateral interstitial infiltrates. Tracheostomy was carried out. The patient was placed on a volume respirator and gradual improvement was noted. Oral intake was started on the seventh postoperative day and consisted of clear fluids, a magnesium-aluminum hydroxide suspension and Lactinex®.* An electrocardiogram showed normal sinus rhythm, and the ST segments were returning to baseline. By the twelfth postoperative day the patient had been advanced to a bland diet. Clinically and radiologically the lungs showed pronounced improvement. Laboratory data were normal with the exception of a hematocrit which remained at 30 to 32 percent. An upper gastrointestinal series with small bowel follow-through was obtained on the eighteenth postoperative day (Figure 2). The proximal small bowel appeared normal. There were changes in the distal small bowel consistent with submucosa edema or hemorrhage.

The patient was discharged on the twenty-first postoperative day. An upper gastrointestinal series two weeks after discharge showed complete resolution of the above findings (Figure 3). In six months of follow-up no symptoms referrable to the gastrointestinal tract occurred.

*A mixed culture of lactobacillus acidophilus and lactobacillus bulgaricus.

Discussion

Hemorrhagic necrosis of the gastrointestinal tract without the presence of demonstrable vascular occlusion has been the subject of numerous case reports over the last 15 years. In 1954, Wilson and Qualheim[13] described a diffuse hemorrhagic process involving the intestinal mucosa in which no vascular occlusion could be found. In 17 of their 20 reported cases the patients had chronic heart disease with varying degrees of congestive heart failure. A close relationship was noted between the onset of abdominal signs and symptoms and the treatment of congestive heart failure with digitalis but an etiologic role was not attributed to this drug. Ende[5] reported six cases of bowel infarction in which no significant mesenteric vascular lesions could be found. All of these patients had definite cardiac failure and were receiving digitalis preparations.

Kligerman and Vidone[7] reviewed all reported

cases of nonocclusive hemorrhagic necrosis of the intestine in the literature and added nine for a total of 109 cases. Cardiovascular disease and a history of congestive heart failure were present in 86 percent of these patients. A review of the individual series contributing to the total number of cases reported by Kligerman and Vidone disclosed that the majority of patients were taking digitalis.[1,3-6,8,13,16]

Musta[9] reported 31 cases of intestinal infarction without vascular occlusion. In 30 of them the patients had heart disease and 25 had chronic congestive failure. Ming[8] found that in his series of 75 patients with hemorrhagic necrosis of the intestine, 79 percent had heart disease with varying degrees of failure. Fifty-seven patients had been digitalized. Williams et al[12] presented seven cases, in six of which the patients had generalized arteriosclerosis and heart disease. Five were taking digitalis and digitalis toxicity was present in one. Sixteen cases were reported by Sorensen and Vetner[11] in 1969. Thirteen were in congestive heart failure and all were receiving digitalis. Digitalis intoxication was present in four.

Gazes et al in 1961 postulated a relationship of nonocclusive mesenteric infarction and digitalis.[16] They reviewed 11 cases and found that all of the patients had heart disease and had received large doses of digitalis. Several were in digitalis toxicity. Stating that the degree of cardiac decompensation varied significantly and conjecturing that if congestive heart failure were the primary cause of this lesion it would undoubtedly be seen more often, Gazes suggested that the "common denominator" was digitalization and digitalis toxicity. In 1964, Polansky and coworkers[18] reported 23 cases of nonocclusive infarction and in 21 of them the patients had mild to severe cardiac failure and were taking digitalis. Twelve patients were definitely in digitalis toxicity, and conditions suggestive of toxicity were present in seven others. They also postulated that digitalis toxicity appears to play an important etiologic role in mesenteric infarction without vascular occlusion.

Fogarty and Fletcher[15] compared the clinical features associated with the 102 cases of mesenteric occlusion with infarction with 18 cases of mesenteric infarction in which no vascular occlusion could be found. A "diagnostic triad" was noted that allowed the two entities to be differentiated. Nonocclusive mesenteric ischemia and infarction were associated with severe congestive heart failure in 89 percent of the cases while digitalis intoxication was present in 83 percent, and hemoconcentration also present in 83 percent. When ischemia and infarction are due to documented vascular occlusion, the figures are 16 percent, 13 percent and 21 percent, respectively. Muggia,[17] also in 1966, reported 11 additional cases of hemorrhagic necrosis of the intestine. All the patients were taking digitalis and eight of them had electrocardiographic changes consistent with digitalis toxicity. Muggia expressed belief that digitalis was an important contributory factor in infarction of the bowel without vascular occlusion and that this was primarily due to a direct effect of digitalis on the mesenteric vessels.

Pierce and Brokenbrough[10] reviewed 140 cases of mesenteric infarction, both occlusive and nonocclusive, and in each group found evidence of cardiovascular disease in 90 percent and low cardiac output in 50 percent. Digitalis was being taken by 90 percent of the patients without mesenteric arterial occlusion compared with 60 percent of those with occlusion. Digitalis intoxication was present in 27 percent without occlusion and in 9 percent with occlusion.

Clinical and pathologic features. The clinical and pathologic findings in all of these cases are similar. The clinical situation is that of a patient in the seventh or eighth decade with cardiovascular disease and congestive heart failure who has sudden onset of severe abdominal pain. Often there is a history of vague prodromal abdominal complaints. Abdominal tenderness, distension, nausea, vomiting and melena are usually present. The severity of the pain is generally out of proportion to the physical findings. Fever and leukocytosis are invariably present. A hematocrit greater than 50 percent is not uncommon, but this will depend on the amount of third space fluid loss and gastrointestinal hemorrhage. Abdominal x-ray films are of minimal value, with signs of mild ileus often being the only demonstrable findings. Abdominal angiography has been advocated by several observers.[13,19] Its primary value, however, has been in helping to explain the pathogenesis of this entity. A positive diagnosis cannot be made by arteriography, though it may be suggested by unequal flow patterns in the mesenteric vessels. All patients should have emergency elective angiography, if possible, to exclude occlusion of the major vessels. The clinical course is rapidly fatal, with shock usually the terminal event. There have

been no previously reported survivors of massive nonocclusive mesenteric infarction.

The small and large intestine at celiotomy or autopsy appear discolored, edematous and dilated. The mucosa is thin, friable and hemorrhagic, with superficial ulcerations often present in the most affected areas. The distribution may be diffuse or segmental and it bears no relationship to the major arterial supply. Arteriosclerotic involvement of the mesenteric vessels is common, but no point of arterial or venous occlusion is evident. Microscopically there is hemorrhage into the mucosa of the bowel, various stages of necrosis ranging from simple distortion of neutrophilic response, engorgement of the mucosal and submucosal veins, and little or no involvement of the muscularis propria and serosa.

Etiology. Hemorrhagic necrosis of the bowel without vascular occlusion is a common finding in dogs dying of hemorrhagic shock. When an animal is bled to a mean arterial pressure of 33 mm of mercury and the pressure is maintained at that level for at least four hours, circulatory failure and death occur.[20] At necropsy, the small bowel mucosa is ulcerated and necrotic. The mechanism producing these lesions in shock states of whatever cause is a stimulation of the sympathetic nervous system due to baroreceptor activity resulting in the release of norepinephrine at postganglionic nerve endings in the skin and viscera. Cutaneous and visceral vasoconstriction subsequently produces a decrease in the size of the circulating vascular space and an increase in total peripheral resistance. Continuing blood flow to the brain and heart is maintained. Prolonged vasoconstriction of the visceral bed ultimately leads to ischemic and tissue necrosis. Approximately 65 perecnt of the total blood flow to the intestinal wall is to the metabolically active mucosa.[21] Severe ischemia consequently produces extensive damage to the bowel mucosal. The canine hepatic venous response secondary to sympathomimetic stimuli is very prominent because of smooth muscular fibrils in the hepatic veins which act as a sphincteric mechanism. Constriction of these muscles produces a noticeable increase in portal venous pressure, which causes mesenteric congestion.[20] Corday and coworkers[3] conducted a series of experiments to determine whether mesenteric or hepatic angiospasm was responsible for the canine gastrointestinal ischemia and necrosis seen in low flow states. They found that during acute hypotension and arrythmias, angiospasm of the mesenteric arterioles occurs and portal venous pressure decreases, suggesting that spasm of the hepatic veins does not play a significant role in producing bowel necrosis. They concluded that with congestive heart failure and cardiac arrythmias, the cardiac output is diminished and hypotension develops. The result is a compensatory vasoconstriction which may be severe enough to cause intestinal infarction.

Humans with nonocclusive intestinal infarction show a variable degree of congestive heart failure at the onset of abdominal complaints. Although most such patients have heart disease with a history of failure, few are actually in severe failure when infarction occurs. It is this fact that has led several investigators to postulate that, in addition to a low cardiac output, an arteriosclerotic and already compromised mesenteric vasculature must exist for nonocclusive infarction to take place.[5,7,15]

The law of La Place has been offered as a possible explanation for the diminished splanchnic blood flow which leads to mesenteric infarction without occlusion.[6] This physical law relates total tension in a vessel wall to its radius and the hydrostatic pressure within it. The important physiologic implication is that blood vessels under vasomotor tone have a "critical closing pressure." If the pressure in the arterioles of a vascular bed falls below this critical pressure, there will be an abrupt cessation of all blood flow. This is presumed to be the mechanism in the arterioles of the mesenteric vascular bed and results in ischemia with ultimate progression to infarction.

The time at which the patients with nonocclusive hemorrhagic necrosis present in clinical shock is variable. In some cases the onset of shock follows the appearance of abdominal pain, while, in others, it is a terminal event or does not occur at all. Only one of the 11 patients reported by Ming[8] was in shock before the onset of abdominal pain. Musa[9] observed that shock was present in only 16 of 31 patients, seven of whom had abdominal signs and symptoms before the onset of shock. Shock was the initial event in nine instances. Theoretically, any type of vascular collapse with compensatory vasoconstriction may precipitate bowel ischemia and infarction. However, Musa concluded that in humans there must be pre-existing cardiac disease.

Fogarty and Fletcher[15] noted three persistent findings in nonocclusive mesenteric ischemia—

severe congestive heart failure, hemoconcentration, and digitalis intoxication. They suggested that these factors might be etiologically related to the development of the disease. Because of vomiting and third-space fluid loss, the hematocrit of these patients is usually high. Elevation of the hematocrit in the face of vasoconstricted and arteriosclerotic vessels offers a significant resistance to flow and may lead to ischemia.

The extracardiac manifestations of digitalis have been the subject of several investigations. The peripheral vascular effects of digitalis were studied by Ross et al.[21,22] By removing the heart from the circulation and thereby eliminating the positive inotropic effect of the drug from consideration, significant arterial and venous vasoconstriction was demonstrated through use of therapeutic doses of digitalis. Ganglionic blockade or adrenalectomy did not prevent this response. They concluded digitalis has a direct action on vascular smooth muscle which results in both arterial and venous vasoconstriction. Using a patient on cardiopulmonary bypass, Braunwald and coworkers[23] studied the effects of digitalis on systemic vascular resistance and confirmed these direct systemic vasoconstriction properties in man. Mason and Braunwald,[24] also studying the effects of digitalis on forearm vascular resistance and venous tone in normal subjects, demonstrated a direct constricting action of digitalis on forearm vasculature in normal subjects.

Ferrer et al[25] found an intensification of splanchnic vasoconstriction following digitalis therapy in patients with ventricular failure. Mason, however, repeating his digitalis studies on forearm vascular resistance in patients who were in heart failure, showed decreased vascular tone and increased blood flow secondary to the digitalis-induced improvement in cardiac output, and subsequent decrease in reflex arteriolar and venoconstriction. This vasodilatory action is indirect and apparently overrides the direct vasoconstrictor effect. This improvement in myocardial contractility and cardiac output does not overcome the splanchnic vasoconstriction demonstrated by Ferrer et al. They postulated that the "splanchnic vasoconstrictor driver of failure" may be altered by a mechanism other than the baroreceptor system or that digitalis has a selective vasoconstrictor effect on the splanchnic vessels.

Corday et al[3] showed that cardiac arrythmia in dogs can produce mesenteric ischemia by lowering cardiac output and initiating a compensatory vasoconstriction. Since arrythmia is intimately associated with digitalis toxicity, this may be one of the ways in which digitalis intoxication produces mesenteric ischemia. This indirect mechanism is probably not as significant as the direct vasoconstrictor action on the splanchnic vessels.

The digitalis intoxication seen in the case herein reported could have produced nonocclusive mesenteric infarction in several ways. There was a three-day history of persistent vomiting, initially due to the well known central effect of digitalis, leading to dehydration and hemoconcentration resulting in an increased resistance to mesenteric flow. The cardiac arrythmia secondary to intoxication along with the contracted blood volume resulted in decreased cardiac output and compensatory vasoconstriction. Finally, and perhaps most important, was the direct vasoconstrictor action of digitalis intensified by the toxic dose. Each one of these factors, as well as some degree of preexisting congestive heart failure, contributed to the massive nonocclusive mesenteric infarction seen in this case. All of these factors are of significance in the development of this entity. The role of each differs from case to case. It is questionable whether any of these factors alone could produce nonocclusive hemorrhagic necrosis in man. It is important not only to recognize that such a lesion exists, but to understand the circumstances in which it occurs.

Treatment

Successful treatment is based upon early recognition and nonoperative management. Early diagnosis was the major factor in the survival of the patient reported here. Celiotomy should be avoided and the diagnosis made on clinical grounds, but it is often a difficult task to differentiate between occlusive and nonocclusive infarction without the benefit of intraoperative examination. Abdominal selective angiography may be of help in this situation. Should celiotomy be carried out and no point of vascular obstruction demonstrated, a thorough knowledge of the disorder will prevent fruitless, prolonged search and needless resection.

Nonoperative management includes close monitoring of the blood pressure, pulse rate, urine output, central venous pressure, and hematocrit. All fluid losses should be immediately replaced with the appropriate intravenous solutions. Hemoconcentration must be corrected. Low modecular

weight dextran or heparin or both are suggested as a means of enhancing mesenteric blood flow.

The use of vasoactive drugs has been proposed in a number of reports.[2,12,20] Circulatory support through the use of vasopressors such as norepinephrine is inconsistent with what is known of the pathophysiology of nonocclusive mesenteric infarction. Vasoconstriction of whatever cause is widely accepted as the precipitating event. Any agent that increases splanchnic vasoconstriction is detrimental to the survival of the bowel. Isoproteronol, a beta adrenergic stimulating agent, and phenoxybenzamine, an alpha adrenergic blocking agent, have been considered efficacious in the treatment of low output shock, as their effect is to increase cardiac output. These agents should never be used instead of or before aggressive fluid replacement. Intravenous fluid replacement, closely monitored with central venous pressure or pulmonary artery wedge pressure, is necessary for survival and is indicated even in the face of a history of cardiac decompensation.

Many of the patients are taking digitalis. It is important to realize that increasing the dose or giving additional doses in an effort to improve myocardial contractility can easily result in toxicity because of the pronounced fluid and electrolyte shifts associated with mesenteric infarction. Because of this and reports linking digitalis and its direct peripheral vasoconstriction to nonocclusive mesenteric infarction, discontinuation of digitalis therapy should be strongly considered. If toxicity is present, it should be promptly treated.

Finally, broad spectrum antibiotic coverage is essential because of the necrotic state of the intestinal mucosa. The mucosal barrier has been destroyed, leaving these patients very susceptible to massive sepsis.

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Refer to: St. Geme JW Jr: Seminars in infectious disease—A new look at infectious gastroenteritis. West J Med 121: 456-461, Dec 1974

Seminars in Infectious Disease

A New Look at Infectious Gastroenteritis

JOSEPH W. ST. GEME, JR., MD, *Torrance, California*

IN RATHER SHARP CONTRAST to the exploration of other anatomical loci of infectious disease, the accumulation of significant biologic information concerning gastrointestinal infection has been slow. Whereas the etiologic agents and the epidemiologic and pathologic principles involving acute respiratory disease have become well defined during the past 20 years, not until very recently has there been any new knowledge of infectious gastrointestinal disease. During the past several years, gastrointestinal infections have been analyzed with exciting new tools which have elucidated provocative and important pathobiologic data.

Etiologic and Epidemiologic Perspectives of the Past

Moffett and his colleagues[1] reported that Salmonella and Shigella were unimportant causes of winter gastroenteritis in the Chicago area. However, 10 percent of their patients with diarrhea were found to have enteropathogenic E. coli (EEC) in their stools, while this organism could be recovered in only 1 percent of control children. These workers also developed data supporting the notion that adenoviruses are significant gastrointestinal pathogens. Seventeen percent of patients with diarrhea shed various adenovirus serotypes—but a substantial 5 percent of control subjects also excreted these viruses.

Yow and her coworkers[2] have probed the etiologic spectrum of gastroenteritis in the Southwestern United States with extensive, continuous studies for many years. With the possible exception of some unserotyped strains of group A coxsackieviruses, they failed to implicate enteroviruses or adenoviruses as significant gastrointestinal pathogens in the Houston area. Although these viruses were isolated from the feces of 27 percent of study patients, 19 percent of control subjects also shed the same viruses; hence no etiologic significance can be attributed to the isolates. In contrast to the experience in Chicago where approximately 10 percent of infants with diarrhea yielded enteric bacillary pathogens (ECC in virtually all instances), in Houston 30 percent of patients shed bacterial pathogens, half of which were EEC with the remaining pathogens almost equally distributed between Shigella and Salmonella species. Only 2 percent of control subjects carried some of these organisms in the gut.

The earlier studies of Ramos-Alvarez and Olarte[3] in Mexico City had indicated that enteroviruses and adenoviruses may be significant causes of infectious gastroenteritis. They isolated viruses from the stools of 58 percent of patients, most of which were unclassified enteroviruses, but also included were echoviruses, polioviruses, coxsackieviruses and adenoviruses. Only 13 percent of control subjects shed these viruses. Strikingly different rates of isolation from patients with diarrhea were recorded for adenoviruses, echoviruses and the untyped enteroviruses. Hence, these studies offer some modest support for the observation in Chicago which implies an etiologic role for adenoviruses. Accepting for the moment that there is a significant temporal relationship between adeno-

From the Department of Pediatrics, Harbor General Hospital, Torrance, and University of California, Los Angeles, School of Medicine.

Submitted June 25, 1974.

Reprint requests to: J. W. St. Geme, Jr., MD, Department of Pediatrics, Harbor General Hospital, UCLA School of Medicine, 1000 West Carson Street, Torrance, CA 90509.

viruses in the stool and gastroenteritis, one might speculate that adenoviruses do not in fact produce gastroenteritis but instead are reactivated from latent foci in intestinal lymphoid tissues consequent to the physiologic changes in the gut induced by another primary pathogen.

Enteric bacillary pathogens were recovered from 46 percent of patients and 14 percent of control subjects in Mexico City. Thus, as was true in Houston, approximately 30 percent of patients experienced bacillary dysentery; but in Mexico City only Salmonella and Shigella were important and statistically significant pathogens. The rate of recovery of EEC was similar in patients and control subjects—approximately 15 percent.

An extensive pathophysiologic study of infants with diarrhea and hypertonic dehydration in Buffalo, although unrewarding in the search for pathogens, showed that the majority of cases occurred during the winter months.[4] These studies suggest that the enteric bacteria and viruses which have been discussed above, while capable of producing isolated illnesses and occasional small outbreaks, may be unimportant causes of the acute infectious gastroenteritis which occurs throughout most of this country, often in epidemic proportions and frequently during the winter months. One must suggest that the real pathogen(s), whether bacterial or viral, has eluded the investigative efforts and detection systems of the past 15 or 20 years.

Metabolic and Physiologic Considerations

In the previously mentioned Buffalo studies, the electrolytic composition of feces was carefully analyzed and it was found that the sodium concentration in the stools of infants with hypertonic dehydration was only 10 to 30 mEq per liter.[4] Potassium loss was slightly greater. On the other hand, the electrolyte pattern in the stools of cholera patients resembles that of plasma, with the exception of potassium (which is four- to eightfold greater in cholera stools) and bicarbonate, which may approach twice the concentration of plasma.[5] Children with cholera lose slightly less sodium in the stool. So, at one extreme is the low concentration of fecal sodium in patients with winter gastroenteritis and hypertonic dehydration (about 20 mEq per liter) while at the other extreme children with cholera produce stools containing 90 mEq per liter of sodium.

Recognition of these electrolyte patterns has permitted the development of more appropriate physiologic restitution of the altered solute and fluid metabolism in these patients. Since the principal problem with hypernatremic gastroenteritis is excessive water loss, metabolic repair is conducted with hypotonic polyelectrolyte solutions. While lactated Ringer's solution (Na 130 mEq per liter) provides suitable correction of cholera in adults, where fecal losses of sodium approach 135 mEq per liter, a less concentrated solution (Na 90 mEq per liter) works more effectively in children.[5] Some of the standard electrolyte solutions of many years ago—lactated Ringer's solution, for example—contain too little potassium (4 mEq per liter) and freely available bicarbonate (28 mEq per liter, as lactate) to replenish the striking losses in cholera.

The biochemical pathogenesis of the excessive sodium loss in cholera stools is clear and logical, and may be provocatively instructive to clinicians caring for patients in the continental United States. Vibrio cholerae (El Tor) bacillus elaborates a toxin which switches on adenyl cyclase in the intestinal cell membrane, increasing the concentration of cyclic adenomonophosphate (AMP) and altering the permeability of surface cell membranes to sodium flux into the lumen of the gut.[6] Another cell membrane enzyme, sodium-potassium-dependent adenotriphosphatase (ATPase), also regulates sodium loss into the gut. Decreased levels of this enzyme precede sodium leak. Of considerable interest is the observation that a coronavirus, which produces transmissible gastroenteritis of piglets, erases this enzyme from the surface of the gut cells.[7]

In this same natural porcine gastrointestinal infection, the disaccharide-splitting enzymes, lactase and sucrase, are also eliminated or reduced at the villous, lumenal surface of the gut. These enzymatic deletions are transient, fortunately, and have been described in human illness as well. Lifshitz and his coworkers[8] reported that almost 80 percent of children with acute gastroenteritis incur transient lactase intolerance. In our own experience, we have noted this complication very infrequently. Transient malabsorption of fat and xylose may also occur after gastroenteritis in adults.[9]

Pathogenetic Implications

Cholera organisms produce a biochemical disturbance in the small bowel but do not invade the mucosa nor evoke an inflammatory response. Some strains of E. coli behave in a similar man-

ner.[10] Other strains of E. coli penetrate the wall of the small intestine, as do Shigella organisms, establishing a destructive inflammatory process consistent with the mucus and blood which typify the diarrheal stool in many of these infections. Salmonellae penetrate more deeply into the mucosa of the small and large intestine, provoking a more extensive erosive inflammatory disease and occasionally a substantial efflux of fluids.[11] With the exception of Shigella dysenteriae (the Shiga bacillus), these invasive bacilli do not produce enterotoxins and therefore one might not anticipate the profound, selective sodium loss into the gut so characteristic of cholera or cholera-like disease. The Shiga bacillus possesses a cytotoxin which may account for some of the intense colitis, but the crucial factor in the virulence of this organism is its ability to penetrate the gut wall.[12]

That shigellosis is a highly communicable disease is not surprising since only 10 to 100 bacterial cells are required to establish human infection.[13] Salmonella infections result from the ingestion of 100,000 organisms, and 1,000-fold greater concentrations of E. coli and Vibrio cholerae are needed to initiate gastrointestinal infection.

As has already been suggested for some viruses recovered from the gastrointestinal tract, many people may carry enteric bacillary pathogens in the gut but at concentrations too low to produce illness. An intriguing story of joy-riding pigs suggests that stress of various sorts may permit rapid multiplication of these submerged potential pathogens.[14] Following a prolonged ride in a Salmonella-free vehicle, a crowded group of pigs that had pathogen-free feces before the ride, had gastrointestinal tracts laden with Salmonella organisms after the ride. The organisms could have come from no other place than the carefully regulated microbial flora of their own guts. Perhaps one of the most important components of autonomous control of and resistance to intestinal pathogens is the diverse population of aerobic and anaerobic microbes within the distal small intestine and colon. These organisms elaborate bactericidal colicins and short-chain fatty acids which delicately regulate the intrusion or endogenous reproduction of pathogenic bacilli.

The only reported case of cholera in the United States during the past year occurred in a man with partial gastrectomy—an eloquent illustration of the importance of gastric volume, acidity, and normal emptying time in innate resistance to intestinal pathogens.[15] One should note that polioviruses can invade the intestine because by their characteristic acid-resistance they can pass through the stomach unscathed. Gastrointestinal hypermotility is also an important mechanism for the elimination of enteric pathogens. To this point, a recent report cites the prolongation of microbial shedding in persons treated with Lomotil® for bacillary dysentery.[16] Coproantibodies or secretory IgA antibodies provide classic immunologic control within the gut. The importance of these antibodies is clearly delineated by the near eradication of virulent poliovirus from the community following the use of attenuated vaccine (Sabin). Killed vaccine (Salk) prevented the onset of viremic paralytic disease but polioviruses continued to flourish within the sanctuary of the intestinal lumen. Because attenuated virus replicates within the gut and gut lymphoid tissue, local antibody is produced.

Therapy: Adventure or Misadventure

While there is no controversy surrounding the use of antibiotics in the treatment of typhoid fever, the choice of antibiotic has become more complex. In the past, chloramphenicol has been judged by most authorities to be preferable. Recently, strains of Salmonella typhosa have been isolated which are clearly resistant to chloramphenicol but retain susceptibility to ampicillin.[17] To date, these strains have originated in Mexico. They carry and transmit an extra piece of episomal DNA, or so-called plasmid, which specifies resistance to a wide range of antibiotics and codes for the production of resistance transfer factor (RTF).[18] These genes affect the resistance to chloramphenicol as well as to sulfadiazine, streptomycin and tetracycline by diverse biochemical processes of enzymatic inactivation and inhibition of antibiotic incorporation by the bacterium. RTF promotes the transfer of drug resistance genes from one bacterium to another by conjugation. The majority opinion today suggests that other Salmonella infections be treated conservatively without the use of antibiotics. Several studies indicate that ampicillin treatment of Salmonella dysentery exerts no beneficial effect on the amelioration of symptoms and in fact permits prolonged excretion of the enteric pathogen.[19,20] Presumably, ampicillin is more effective in deterring the multiplication of the normal gut organisms, which if left to their own regulatory devices for controlling the microbial population would subdue intruding pathogenic bacilli.

Several years ago it appeared that the antimi-

crobial management of Shigella dysentery should be quite different from that of salmonellosis. Shigella sonnei and flexneri infections of the gastrointestinal tract were significantly modified by ampicillin therapy.[21,22] Diarrhea, noxious symptoms and pathogens disappeared more quickly with treatment. The clinical, pharmacologic, and bacteriologic observations of Haltalin and his colleagues[23] were convincing and, despite the fact that many patients with shigellosis were asymptomatic by the time bacteriologic verification of the infection was obtained, clinicians began to look more favorably upon antibiotic treatment of shigellosis. Since so few Shigella organisms are required to initiate secondary waves of infection within a populace, eradication of Shigellae more quickly with antibiotics would seem advisable. To their great credit, and very fortunately, the Dallas investigators continued to monitor Shigella infections in their locale and learned that these organisms were rapidly acquiring resistance to ampicillin.[24] The culprits are episome-bearing strains, resistant to ampicillin, which flourished with the selective pressure of ampicillin treatment of many Shigella infections in the community. Microbial conjugation allowed the RTF-promoting episomal DNA to flow from the increasing population of resistant organisms to previous susceptible strains.

The predominant Shigella pathogens in the United States are S. sonnei and S. flexneri. Although transiently discomforting, illness caused by them is ordinarily benign. Infection with the Shiga bacillus S. dysenteriae may be quite severe and occasionally fatal. Recently, infection with this more virulent species of Shigella has occurred in this country, and the source seems to be Mexico. Interestingly, the pattern of antimicrobial resistance of these isolates is the same as that of the chloramphenicol-resistant strains of Salmonella typhosa which have been imported from Mexico, further highlighting the fact that episomal DNA may be shared among several species of enteric organisms.

Traditional treatment of EEC gastrointestinal colonization and infection has included the use of antibiotics, usually neomycin and recently ampicillin. The therapeutic efficacy of ampicillin in this setting is unresolved and currently there is reason to suggest that protracted neomycin therapy may not only prolong the residence of these occasional pathogens in the gut but also condition the appearance of other enteric pathogens, such as Salmonella and Shigella.[23,25]

New Gastrointestinal Pathogens

In our introductory remarks we suggested that a new pathogenic perspective of acute infectious gastroenteritis had emerged during the past few years.

Utilizing an exciting but laborious bio-assay technique, several groups of investigators have discovered a vast array of new serotypes of E. coli which seem to be of great importance in the causation of human gastroenteritis.[10,26] These strains of E. coli elaborate an enterotoxin similar in physiologic action to cholera toxin. The E. coli enterotoxin produces a significant shift of fluid and electrolyte from the wall of a closed loop of infant rabbit gut into the lumen. A somewhat simpler technique for the bio-detection of toxigenic strains has recently been described: In this technique, cultivated adrenal cells are induced to elaborate corticosteroid and undergo cytodestruction.[27] Gorbach and his colleagues[28] examined 600 strains of E. coli recovered from the stools of 29 children from Chicago who had acute gastroenteritis. In this energetic study, using the intestinal loop assay, these investigators identified species of toxigenic E. coli (TEC) in 20 children, surpassing rather strikingly the isolation of standard strains of EEC from the remaining patients. TEC, serotypes 0148:K:H28 and 0142:K86:H6, have been incriminated as the cause of "traveler's diarrhea" or "Montezuma's revenge." These newly identified pathogens have been observed to produce much of the infantile gastroenteritis in England and Scotland. Considering the cholera-like biologic features of these pathogens, it is not surprising that mortality rates of almost 40 percent have been reported from Mexico following the onset of TEC gastroenteritis.

Some strains of EEC elaborate toxin. By no means should one conclude that E. coli which are not agglutinated by EEC typing sera are uniformly toxigenic. They are not. There are many strains of E. coli which may be identified in a few special laboratories by their agglutination with antisera directed against the O, K and H antigens of the E. coli bacterium. In the past only seven strains of EEC were considered important gastrointestinal pathogens, namely, serotypes 026:B6, 055:B5, 086:B7, 0111:B4, 0112:B11, 0119:B14, 0124:-B17, 0125:B15, 0126:B15, 0126:B16, 0127:B8, 0128:B12, and commercial antisera were developed which permit hospital laboratories to identify them with ease. From a pathogenic point of view this is only the tip of the iceberg. Further-

more, non-toxigenic E. coli may also be pathogenic. Inspecting the intestinal loop assay system histologically discloses that some strains which are non-toxigenic penetrate the gut wall and produce significant inflammatory destruction of intestinal villi and crypts. This pathologic change is similar to that produced by Shigella organisms and very likely the classic signs and symptoms of shigellosis —diarrhea, fever, cramps, tenesmus and bloody mucoid stools—may also be evoked by strains of E. coli untypable by the readily available EEC typing sera. In infant rabbits, toxigenic strains produce no histologic alteration of the gut. The cholera-like illness produced by these organisms, characterized by profuse watery stools, is mediated in a biochemical rather than structural fashion by the resultant activation of adenyl cyclase in the membrane of the intestinal epithelial cell and increased concentration of cyclic AMP within the gut cell.

Heretofore, approximately 70 to 80 percent of all cases of acute infectious gastroenteritis were etiologically obscure. The discovery of numerous toxigenic and penetrating serotypes of E. coli, exclusive of the classic EEC, suggests that 20 to 30 percent of gastrointestinal infections may be caused by these organisms. Many investigators have suggested that at least half of these illnesses are viral in nature but the true gastroenteritis virus could not be detected by standard techniques. A dramatic breakthrough has evolved during the past five years and a small, 27 nanometer, acid-resistant virus has been isolated which looms as the principal cause of acute infectious non-bacterial gastroenteritis.[13,29] Experimental infections in volunteers have indicated that this virus produces diarrhea or vomiting or both following a very short incubation period of 24 to 48 hours. Nausea, low fever, abdominal cramps, headache and myalgia accompany the natural and experimental illness, fully qualifying this virus as the culprit involved with so-called winter vomiting disease or gastrointestinal "flu." The original strain of virus was recovered from an outbreak in Norwalk, Connecticut and bears the label of the Norwalk strain. The virus can be propagated in human fetal intestinal organ culture and retains human infectivity following serial passage. By using convalescent sera from infected persons, the virus can also be detected in fecal specimens by immune-electron microscopy.[30] The virion may also be detected in electron micrographs of biopsy specimens of duodenum; and, by analysis of both duodenal and fecal smears, the Australians have observed that 80 percent of children with sporadic acute non-bacterial gastroenteritis in Melbourne carry this virus.[31]

Transient malabsorption of xylose, lactose and fat has been well documented as a component of natural and experimental infection with the Norwalk virus.[32,33] Not unexpectedly, biopsy of the upper small intestine has disclosed the histologic alteration of classic sprue-like illness, with blunted villi, submucosal lymphoid infiltrate, and diminution of dissacharide-splitting enzymes at the brush border of gut epithelial cells.

Epidemiologic observations within closed communities suggest that there may exist several serotypes of the Norwalk prototype virus, with sufficient antigenic disparity to preclude life-long immunity following an initial episode of illness.[34] This should not be surprising as one reflects upon the recurrence every few years or so of explosive winter vomiting (and diarrhea) disease which sweeps briskly through families, with intervals between the index and secondary cases of only a day or so. If indeed there is only one Norwalk virus, immunity which is largely local and mediated by secretory IgA neutralizing antibody may not persist in sufficient magnitude to prevent reinfection. This is certainly true for the large segment of viral infections which we endure in another surface organ, the respiratory tract.

Epilogue

The excitement of critical discovery has only recently swept into this area of human disease. One hopes that the new biology of new pathogens and the lessons learned from traditional pharmacologic manipulations of the microbial environment will lead us toward more innovative and effective methods of prevention and cure.

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Medical
PROGRESS

Refer to: Keeffe EB, Katon RM, Chan TT, et al: Pseudomembranous enterocolitis—Resurgence related to newer antibiotic therapy (Medical Progress). West J Med 121:462-472, Dec 1974

Pseudomembranous Enterocolitis

Resurgence Related to Newer Antibiotic Therapy

EMMET B. KEEFFE, MD, RONALD M. KATON, MD, TSOI T. CHAN, MD, CLIFFORD S. MELNYK, MD, *and* JOHN A. BENSON, JR., MD, *Portland*

Six patients with pseudomembranous entercolitis were seen at one institution over a six-month period. Clindamycin therapy preceded the diagnosis in all six patients and possibly caused the disease in five cases. Common clinical features included diarrhea, abdominal pain, fever, leukocytosis, radiographic findings of large bowel dilatation with mucosal thickening and a characteristic sigmoidoscopic or gross pathologic demonstration of discrete yellow-white plaques on an otherwise normal mucosa. Complications included toxic megacolon and sigmoid colon perforation. Two of the six patients died. The literature since 1970 is tabulated to clarify the clinical and pathological features of pseudomembranous enterocolitis associated with newer antibiotic therapy. Lincomycin and clindamycin are strongly implicated in the recent resurgence of this formerly rare variety of colitis.

NONSPECIFIC GASTROINTESTINAL COMPLICATIONS, including diarrhea, commonly follow antibiotic therapy, and symptoms rapidly subside when therapy is discontinued.[1] Diarrhea appears to be especially common in patients receiving lincomycin and clindamycin, the estimated incidence ranging from 20 to 50 percent for the former[2] and 2 to 24 percent for the latter.[3,4] The great majority of antibiotic-associated diarrheal syndromes have been considered to be nonspecific without associated morbidity and the occurrence of overt colitis, either pseudomembranous or ulcerative, to be uncommon. However, a recent prospective study of 100 hospitalized patients who received clindamycin revealed a substantial incidence of diarrhea (24 percent) and of colitis (10 percent).[4] Many recent reports have noted the association of pseudomembranous enterocolitis with antecedent lincomycin or clindamycin therapy.[5-15] In addition a syndrome clinically and sigmoidoscopically indistinguishable from acute ulcerative colitis has been reported less frequently as a sequel to these same antibiotics.[2,16,17]

A recent increase in the frequency of pseudomembranous entercolitis has also occurred at the University of Oregon Medical School. Six cases have been recognized in the six months preceding May 1974. The purpose of this report is to dis-

From the Division of Gastroenterology, Departments of Medicine and Pathology, University of Oregon Medical School, Portland.

Reprint requests to: E. B. Keeffe, MD, Department of Medicine, Oakland Naval Regional Medical Center, 8750 Mountain Blvd., Oakland, CA 94627.

cuss these six cases and to summarize the recent literature concerning antibiotic-associated enterocolitis. The clinical features of this syndrome need to be widely disseminated since early diagnosis by sigmoidoscopy, cessation of the antibiotic and supportive therapy appear to improve the outcome.[4]

Reports of Cases

CASE 1. A 74-year-old diabetic man was admitted to hospital for evaluation of ischemic foot pain. After preoperative angiography, a left femoral-popliteal bypass graft was done. The postoperative course was complicated by moderate hypotension. Two weeks later his left lower leg was amputated because of persistent ulceration. Nafcillin (4 grams administered intravenously each day) and gentamycin (180 mg administered intramuscularly each day) were started during the operation and continued for ten days. In addition, two doses of clindamycin (a total of 1,200 mg administered intravenously) were given on the second postoperative day. Postoperatively, the patient was fed only by nasogastric tube. One week after the course of antibiotics was completed, diarrhea with abdominal distention, fever and leukocytosis to 22,000 per cu mm developed. Sigmoidoscopy revealed an erythematous mucosa with discrete yellow-white membranes. Serial abdominal films showed colonic dilatation with mucosal thickening initially and later dilatation of large and small bowel with air-fluid levels. Stool cultures yielded Citrobacter species. Administration of Lomotil® (diphenoxylate hydrochloride and atropine) and cessation of nasogastric feedings failed to control the diarrhea. Ten days after the onset of diarrhea, a subtotal colectomy and feeding gastrostomy were done because of persistent toxicity and diarrhea. Pathologic study of the colon revealed pseudomembranous colitis. Six weeks after the colectomy, the patient died with recurrent infections, poor nutrition, choledocholithiasis and poorly-controlled diabetes mellitus. Postmortem studies showed residual changes of pseudomembranous enterocolitis of both the small and the remaining large bowel.

CASE 2. Anorexia, nausea, fever, chills, abdominal pain and bloody diarrhea with mucus developed suddenly in a 35-year-old woman. Gastroenteritis was diagnosed and treated with a ten-day course of ampicillin administered orally. The symptoms transiently improved but then worsened approximately ten days after stopping ampicillin. Admitted to another hospital, generalized abdominal tenderness was noted. Leukocytes numbered 19,000 per cu mm. Sigmoidoscopy revealed friable and granular mucosa which showed acute nonspecific colitis on biopsy. Stool culture grew Escherichia coli. Barium studies demonstrated acute left-sided colitis with a normal small bowel and right colon. Salicylazosulfapyridine (Azulfidine®) and hydrocortisone enemas led to gradual improvement but were both reduced when a rash developed. Her symptoms promptly worsened, and she was admitted to the Medical School Hospital where the clinical and radiologic features of toxic megacolon were present. Sigmoidoscopy revealed an edematous mucosa with no friability and a large amount of yellow mucoid material in the lumen and adherent to the mucosa. Stool culture grew E coli, an intermediate coliform and Bacteroides variabilis. Despite 24 hours of intravenously administered steroids and bowel rest, there was no improvement, so a subtotal colectomy was performed. Beginning one day before operation, ampicillin (8 grams intravenously per day), clindamycin (2,400 mg intravenously per day), and gentamycin (240 mg intramuscularly per day) were given. Pathologic study of the colon showed pseudomembranous colitis. At discharge two weeks later, colonoscopy of the remaining rectum and sigmoid colon disclosed no abnormalities. Reanastomosis of ileum to sigmoid colon was done two months later at which time no evidence of colitis was present.

CASE 3. A 60-year-old white man with chronic obstructive pulmonary disease and squamous cell carcinoma of the larynx received procaine penicillin (1,200,000 units administered intramuscularly each day) during the first ten days of hospitalization for pneumococcal bronchitis. A routine sigmoidoscopy showed only internal hemorrhoids and a small adenomatous polyp. Two weeks after completion of penicillin therapy, a laryngectomy with left radial neck dissection was done. Beginning with the operation, the patient was treated with a seven-day course of clindamycin (1,800 mg daily administered intravenously for three days and orally for four days). Eight days after completing clindamycin therapy, fever, nausea, vomiting and diarrhea developed, associated with a leukocyte count of 24,500 per cu mm. Transient spontaneous improvement occurred, and the patient was discharged, only to return after ten days with complaint of persistent fever, abdominal pain and frequent watery diarrhea. Readmission data included a leukocyte count of 30,000 per cu

TABLE 1.—*Literature Regarding Pseudomembranous Colitis from 1970 to April 1974*

AUTHOR, YEAR	PATIENT NUMBER	AGE	SEX	ANTIBIOTIC, ROUTE OF ADMINISTRATION, DURATION OF USE (DAYS) (*)	INTERVAL FROM INITIATION OF ANTIBIOTIC TO DIARRHEA (DAYS)	UNDERLYING DIAGNOSES	STOOL CULTURE	SIGMOIDOSCOPY (†)	BARIUM ENEMA	HISTOLOGY (‡)	THERAPY (§)	OUTCOME
Groll, 1970	1	52	F	Neomycin, O, 7-10 Chloromycetin, IV, 6 Erthromycin, IM, ?	0 0 0	Good health with intermittent diarrhea for 20 yrs.	NEG	PMC	Dilation and irregularity of colon	PMC	1, 2, 3	Died
"	2	20	F	Ampicillin, O, 10	10	Pregnancy Urinary tract infection	NEG	PMC	---	PMC	1, 2, 3, 4	Survived
Benner, 1970	3	23	F	Lincomycin, O, 10	4	Pregnancy Tooth infection	Proteus morganii	PMC	Pseudopolyps and mucosal destruction, primarily right colon	PMC	1, 2, 5 (Lactinex, buttermilk)	Survived
"	4	38	F	Lincomycin, O, 14	5	Salmonella carrier	Proteus morganii	PMC	---	---	1, 5 (Lactinex, buttermilk)	Survived
"	5	44	M	Lincomycin, O, 7	3	Pharyngitis	Proteus morganii	PMC	Diffuse mucosal distruction	---	1, 5 (Lactinex, buttermilk)	Survived
Ecker, 1970	6	38	F	Lincomycin, O, 10	12	Sinusitis	E. coli Proteus Klebsiella-aerobacter S. faecalis	PMC	---	PMC	1, 2, 3, 5 (Fecal enemas)	Survived
Cohen, 1973	7	22	F	Clindamycin, O, 7	<7	Pregnancy Upper respiratory infection	NEG	PMC	Diffuse mucosal disease, primarily right colon	Nonspecific inflammation	1, 2	Survived
"	8	56	M	Clindamycin, O, 5	3	Pacemaker power pack replacement	NEG	PMC	Normal	Nonspecific inflammation	1, 5 (Nystatin)	Survived
"	9	73	F	Ampicillin, O, ? Clindamycin, O, 7	21 7	Septic joint	NEG	PMC	Negative	Nonspecific inflammation	---	Survived
Shimkin, 1973	10	70	F	Clindamycin, ?, ?	>5	?	NEG	PMC	Diffuse colitis	PMC	1, 2, 3	Died
"	11	34	F	Clindamycin, O, 7	14	Diabetes mellitus Otitis media	NEG	PMC	Diffuse colitis	PMC	1, 2	
Schapiro, 1973	12	49	M	Ampicillin, O, 5	<11	Hypertension Heart failure Urinary tract instrumentation	NEG	PMC	Diffuse mucosal irregularity and edema	PMC	1, 2	Died
"	13	53	F	Lincomycin, O, 13	13	Bronchitis	NEG	PMC	Diffuse ulcers, edema, spasm, and pseudopolyps	PMC	1, 2	Survived
"	14	44	F	Tetracycline, O, 7	3	Viral bronchitis and pneumonia	NEG	UC	Diffuse ulcerating colitis	---	1	Survived
"	15	44	F	Lincomycin, IM, 2 Streptomycin, IM, 2	9	Upper respiratory infection Bronchiectasis	---	UC	Normal	---	---	Survived
Manashil, 1973	16	21	F	Clindamycin, O, 5	5	?	---	UC	Mucosal irregularity and edema, primarily right colon	Nonspecific colitis	1, 2, 5 (Azulfadine)	Survived
"	17	25	F	Lincomycin, O, 5	8	Tonsillitis	---	PMC	Right-sided colitis	---	1, 2, 5 (Azulfadine)	Survived
"	18	53	F	Lincomycin, O, ?	4	?	---	PMC	Diffuse colitis, primarily left-sided	---	1	Survived
Scott, 1973	19	57	M	Lincomycin, ?, ?	15	Mitral incompetence Valve replacement Bact. endocarditis	?	PMC	?	PMC	?	Died
"	20	59	M	Lincomycin, ?, ? Penicillin, ? Tetracycline, ? and IM, 8	?	Acute aortic incomp. Cardiac arrest Cardiac failure Bronchogenic carcinoma Right upper lobectomy	?	PMC	?	PMC	1, 4	Survived
"	24	64	M	Lincomycin, ?, ?	18	Fracture of femur Internal fixation	?	PMC	?	PMC	?	Survived
"	25	51	M	Lincomycin, ?, ? Cloxacillin, ?	11	Facial erysipelas	?	PMC	?	PMC	?	Survived
"	26	67	M	Lincomycin, ?, ?	about 21	Acute bronchitis Mild diabetes	?	PMC	?	PMC	?	Died
Tully, 1974	27	68	M	Clindamycin, O, ?	4	Sinusitis	NEG	PMC	Mucosal edema, left colon	---	1, 2	Survived
"	28	80	F	Clindamycin, O, ? Loridine, IM, ?	1	Sore throat	---	PMC	Diffuse ulceration (led to toxic megacolon)	---	1, 2	Died
"	29	43	M	Lincomycin, O, ? Penicillin, O, ?	4	Pleurisy	NEG	PMC	Nodularity, edema and ulceration of left colon	---	1, 2, 5 (Mycostatin)	Survived
"	30	54	F	Lincomycin, O, ?	3	Flu	---	---	---	PMC	1, 4	Died
Tedesco, 1974	31	?	?	Clindamycin, ?, ?	7	Pneumonia	E. coli	PMC	Diffuse colitis or plaques	PMC	?	?
"	32	?	?	Clindamycin, ?, ?	8	Amyotrophic lateral sclerosis	E. coli S. faecalis	PMC	Diffuse colitis or plaques	PMC	?	?
"	33	?	?	Clindamycin, ?, ?	10	Chronic renal failure	E. coli	PMC	Diffuse colitis or plaques	PMC	?	?
Stroehlein, 1974	34	67	F	Clindamycin, O, 14	10	Influenza-like illness	NEG	PMC	Sigmoid colon ulceration	PMC	1, 3	Survived
"	35	53	F	Clindamycin, O, 7	>7	Dental extractions	---	PMC	Rectosigmoid nodularity	Hyperplastic mucosa	1, 2	Survived
"	36	46	M	Clindamycin, O, 5	>5	Dental extractions	NEG	PMC	---	PMC	1, 2	Survived
Keeffe, 1974	37	74	M	Nafcillin, IV, 10 Gentamycin, IM, 10 Clindamycin, IV, 1	15 15 13	Peripheral vascular disease SP bypass graft SP BK amputation	Citrobacter	PMC	---	PMC	1, 4	Died
"	38	35	F	Ampicillin, O, 10 Gentamycin, IM, 3 Clindamycin, IV, 2	0 0 0	Ulcerative colitis	E. coli Intermediate coliform Bacteroides	PMC	Left-sided colitis	PMC	1, 2, 4	Survived
"	39	60	M	Penicillin, IM, 10 Clindamycin, IV and O, 7	40 15	SP laryngectomy COPD	Citrobacter	PMC	---	PMC	1	Survived
"	40	68	M	Cephalothin, IV, 4 Penicillin, IV, 8 Gentamycin, IM, 3 Clindamycin, IV, 6	10 7 7 6	Peripheral vascular disease SP bypass graft	Citrobacter	PMC	---	PMC	1, 4	Survived
"	41	73	M	Clindamycin, IV, 1 Kanamycin, IM, 1 Penicillin, IV, 2 Sulfamethoxazole, O, 0	9 9 9 0	Coronary heart disease SP hiatus hernia repair	NEG	---	Left colon ulceration and edema	PMC	1, 4	Died
"	42	75	M	Clindamycin, IV, 6	5	Pneumonia	NEG	PMC	---	---	1	Survived

*O = Oral; IM = Intramuscular; IV = Intravenous.

†PMC (in Sigmoidoscopy column) = Pseudomembranous colitis (discrete yellow-white plaques on otherwise normal mucosa); UC = Ulcerative colitis (diffusely friable and ulcerated mucosa).

‡PMC (in Histology column) = Pathologic features of pseudomembranous colitis.

§1 = Symptomatic (various combinations of bowel rest, intrevenous fluid or albumin, and cessation of current antibiotic therapy); 2 = Corticosteroids or ACTH; 3 = Antibiotics; 4 = Surgery (usually subtotal colectomy); 5 = Other (as indicated).

mm, scattered discrete yellow-white mucoid plaques on an erythematous colonic mucosa at sigmoidoscopy and a dilated colon with thickened mucosal folds on abdominal films. Multiple stool cultures grew Citrobacter species. Treatment with bowel rest and intravenous fluid and albumin led to rapid clinical, radiologic and sigmoidoscopic improvement. After three weeks in hospital, sigmoidoscopy and rectal biopsy revealed no abnormalities.

Case 4. A 68-year-old white man with a long history of peripheral vascular disease had a left-to-right femoral bypass graft. Postoperatively the patient received multiple antibiotics including cephalosporin (4 grams per day administered intravenously for four days), aqueous penicillin (6 million units per day intravenously for eight days), gentamycin (240 mg per day intramuscularly for three days), and clindamycin (2,400 mg per day intravenously for six days). At the same time, an average of 240 mg of codeine was given daily for pain. On the last day of antibiotic therapy, diarrhea, abdominal pain, fever and leukocytosis were noted. Stool cultures grew Citrobacter species, and sigmoidoscopy showed discrete yellow-white plaques on an erythematous mucosa. Abdominal x-ray studies showed mild dilatation of the colon with mucosal thickening. The patient was initially treated with bowel rest and intravenous fluids, and abdominal pain, diarrhea and fever lessened. His diet was gradually advanced. Twelve days after the onset of diarrhea and five days after initiation of medical therapy, sigmoid colon perforation suddenly occurred. A subtotal colectomy and ileostomy were required, and pathologic study showed pseudomembranous colitis of the entire colon with a discrete sigmoid perforation. When reanastomosis of ileum to sigmoid colon was done two months later, no evidence of pseudomembranous enterocolitis was present.

Case 5. A 73-year-old white man was admitted to hospital for a paraesophageal hiatal hernia and chronic atrial fibrillation secondary to mitral valve and coronary artery disease. A hiatal herniorrhaphy was done for recurrent bleeding and possible incarceration. Antibiotic therapy included two doses of clindamycin (a total of 1,200 mg administered intravenously) and kanamycin (a total of 1,000 mg intramuscularly) the day before operation and also two days of aqueous penicillin (6 million units per day intravenously) postoperatively. Eight days after operation abdominal pain, watery diarrhea, fever and leukocytosis developed. Serial abdominal films showed persistent colonic dilatation and mucosal thickening of the bowel wall, and sigmoidoscopy showed no abnormalities. A barium enema showed mucosal thickening and spiculation of the transverse, descending and sigmoid colon. Stool culture grew only normal flora. Ischemic colitis was suspected, and reoperation was done on the eighteenth postoperative day. The colon was seen to be greatly dilated and inflamed at operation, and an ileostomy, cecostomy and mucus fistula were done leaving the colon in place because of the desperate clinical condition. A cecal specimen showed gross and histologic evidence of pseudomembranous colitis. The postoperative course was complicated and finally sepsis led to death four weeks later, at which time postmortem evidence of pseudomembranous enterocolitis was still present.

Case 6. A 75-year-old white demented male was transferred from a nursing home for progressive disorientation and a fever of 105°F. Pneumonia, possibly caused by aspiration, was treated with clindamycin (2,400 mg per day given intravenously) for six days. Aggressive intravenous fluid therapy was also given to correct the moderate hypotension and hyperosmolar dehydration present on admission. Within 48 hours the patient's mental status, intravascular volume and temperature had returned to normal. Five days after therapy was begun, diarrhea, fever and leukocytosis developed. X-ray films of the abdomen showed mucosal thickening of the left colon, and sigmoidoscopy showed discrete yellow-white plaques studding an erythematous mucosa. Stool culture grew normal flora. Bowel rest and increased intravenous fluids led to improvement. The hospital course was further complicated by staphylococcal sepsis presumably from a pulmonary focus. The patient subsequently transferred back to the nursing home with no residual signs or symptoms of colitis.

Discussion

Pseudomembranous enterocolitis is a disease first recognized in the 1800's and thought to be related to poisons and irritants.[7] Subsequently this disorder has been described in a variety of clinical settings including the postoperative state, after recent antiobitic therapy, debilitating illnesses such as uremia and congestive heart failure, obstruction of the colon, staphylococcal infection of the bowel and ischemia of the gut.[18] These various clinical associations have led to multiple synonyms

TABLE 2.—*Age and Sex of Patients with Pseudomembranous Colitis (42 Total Cases)*

Age	*Patients*
20-29	6
30-39	4
40-49	6
50-59	9
60-69	8
70-79	5
80-89	1
Unknown	3
Sex	*Patients*
Male	17
Female	22
Unknown	3

including postoperative enterocolitis, staphylococcal enterocolitis, antibiotic entercolitis and, the original term, diphtheritic enterocolitis. Whether the term colitis or enterocolitis is used depends upon clinical, radiologic, surgical or pathologic localization. In approximately a third of the cases, the disease is confined to the colon.[18]

The six cases summarized here were all patients admitted to hospital with serious underlying illnesses. Only one of the six patients was under the age of 60. Five of the six patients received multiple antibiotics, and four of the six had recently had operations. Thus, five of the patients had at least two of the three most common etiologic factors important in the development of pseudomembranous enterocolitis: serious underlying illness, antecedent antibiotic therapy and recent surgery.[18] Although clindamycin was administered to all six patients, its role in the pseudomembranous colitis of two cases (Case 3 and Case 6) was highly suspect although recent operation (laryngectomy two weeks previously in Case 3) or serious illness (pneumonia and hypotension in Case 6) could also be remote causes. Clindamycin can be only possibly implicated in three others (Cases 1, 4 and 5). These three patients were elderly, had serious underlying diseases and had received other antibiotics. In addition, Cases 1 and 5 were given clindamycin for only one day. The process in Case 2 initially was consistent with ulcerative colitis, but in the course of the patient's illness ampicillin, recognized as related to the development of pseudomembranous colitis,[5,10] was given and could have been responsible for the subsequent pseudomembranous colitis diagnosed at operation.

In two of the patients, serious complications of colitis developed: toxic megacolon in one and sigmoid colon perforation in the other. In two other patients, subtotal colectomy was required after failure to respond to medical therapy. These latter two patients died, while the remaining four patients recovered. Prompt diagnoses may have been important since both of the patients diagnosed shortly after the onset of symptoms (Cases 4 and 6) survived. The two deaths occurred among the other four patients in whom the diagnoses were delayed more than one week.

The clinical features of these six cases were carefully examined for the presence of a common denominator that might have led to the development of pseudomembranous enterocolitis. Factors not present in more than two patients were excluded as a possible common explanation. These included diabetes mellitus, severe vascular disease, hypotension, congestive heart failure, uremia, digitalis therapy and colonic stasis from drugs or ileus. Although four of the patients were postoperative, their clinical course differed from typical postoperative pseudomembranous enterocolitis, which usually follows an abdominal operation within three to five days.[19] These four patients developed the initial symptoms of colitis 7, 8, 15 and 17 days following their respective operations. Another distinct feature of postoperative pseudomembranous enterocolitis is the more common involvement of the small intestine.[19] In our six cases and also in the cases reported in the literature in which antibiotic therapy was a factor,[5-15] pseudomembranous enterocolitis was always present in the colon. The true frequency of small bowel involvement in antibiotic-associated enterocolitis is unknown since direct visualizaton or pathologic study of the small bowel is frequently not possible. Thus, prior antibiotic therapy, common to all six of the patients, appears to be the most important common denominator.

To better understand the clinical spectrum of modern antibiotic-associated colitis, the literature related to pseudomembranous colitis from 1970 to April 1974 was reviewed. All case reports were tabulated (Table 1) along with our six patients. Abstracts which omitted pertinent details were not included.[4,16,17,20] Thus sufficient data regarding forty-two patients were available for analysis.

Age and Sex

The ages of the patients (Table 2) represent all decades from the twenties to the eighties with a slightly greater frequency in the middle years. There is no reason to suspect that any age should be spared since in the past pseudomembranous

Figure 1.—Colonoscopic appearance of rectal mucosa with discrete yellow-white plaques on a slightly edematous mucosa, Case 3.

colitis associated with previous antibiotic therapy has affected all ages from infancy to late life.[21-23] However, no cases of lincomycin- or clindamycin-associated colitis in the pediatric age range have been reported. The adult population may be at more risk because of the greater frequency of serious underlying illness or because of other unidentified factors. No striking sex predilection was noted (Table 2), and various older literature has shown either male[22,24,25] or female[26] predominance.

Clinical Features

Common to all of our patients was the development of diarrhea, abdominal pain, fever and leukocytosis. Diarrhea in pseudomembranous enterocolitis is usually watery with profuse mucus, and may be associated with rapid loss of large amounts of albumin.[5] Severe diarrhea may result in hypotension, hypokalemia, metabolic acidosis and hypoalbuminemia. The stool of a patient with the disease is not grossly bloody and usually guaiac negative. This is in contradistinction to ulcerative colitis and ischemic colitis, two of the major differential diagnostic considerations. Large and small bowel ileus with abdominal distention frequently occurs.

The diagnosis should be suspected when diarrhea suddenly develops in the setting of current or recent antibiotic therapy or operation. Rapid confirmation by sigmoidoscopy is critical since delay in therapy appears to provide an adverse prognostic factor.[24] The rectal mucosa is studded with discrete yellow-white mucoid plaques (Figure 1) that become confluent in severe cases. The intervening mucosa is generally normal or slightly edematous and erythematous without friability, although typical plaques on a friable mucosa have been reported.[19] In addition, sigmoidoscopy may also reveal a mucosa indistinguishable from ulcerative colitis[2,10,11,16,17] and was present in three cases (Table 3) from the literature review.

TABLE 3.—*Sigmoidoscopic and Barium Enema Findings (42 Total Cases)*

Colitis	*Patients*
Sigmoidoscopy:	
Pseudomembranous	37
Ulcerative	3
Unknown	2
Barium Enema:	
Diffuse	13
Primarily right	4
Primarily left	7

Radiography

Findings on a plain film of the abdomen are nonspecific but usually include colonic dilatation with mucosal thickening. Small bowel ileus may also be present. Uncommonly a toxic megacolon may develop spontaneously in the course of more severe pseudomembranous enterocolitis (Figure 2). We suggest that the barium enema is not needed for diagnosis and is potentially dangerous since it may precipitate toxic megacolon.[13] Most radiologists describing pseudomembranous enterocolitis find the barium enema to be nonspecific with combinations of mucosal edema, ulceration or nodularity (Figure 3) not allowing distinction from other forms of colitis.[9,10,13] However, numerous flat, plaque-like lesions varying in size from 2 to 8 mm are felt by one group to be specific for pseudomembranous colitis.[14] The extent of the colonic involvement on barium enema varied among the reported cases. Diffuse abnormalities were present in 13 patients, while at times the colitis was radiologically localized or much more prominent in the right (4 patients) or left (7 patients) colon (Table 3).

Stool Culture

Stool cultures (Table 1) generally were negative for enteric pathogens or grew normal flora. Notable was the absence of staphylococci which have been implicated in the past.[18,22,24] The role of staphylococcus seems doubtful since the organism

Figure 2.—Toxic megacolon is shown on this plain film of the abdomen from Case 2. Mucosal edema ("thumb-printing") is most evident in the transverse colon, and the small bowel is also dilated.

Figure 3.—Barium enema from Case 5 reveals moderate colonic dilatation with mucosal thickening and spiculation most evident in the descending and sigmoid colon.

is frequently absent not only in cases of pseudomembranous colitis related to antibiotics (Table 1) but also in those cases occurring after operations.[27] In addition, enterocolitis caused by staphylococcus is a clinically and pathologically distinct disease in which pseudomembranes are not present.[25]

Careful stool cultures for anaerobic organisms have not been reported. Their involvement remains to be assessed.

Role of Antibiotics

The association of previous antibiotic therapy with the subsequent development of pseudomembranous enterocolitis has been recognized following administration of tetracycline,[10,24] chlortetracycline,[21,22,26,28] oxytetracycline,[22,24] chloramphenicol,[22,24,26] ampicillin,[5,10] lincomycin,[6,7,10-13] clindamycin[8,9,11,13-17] and penicillin plus streptomycin.[24] No prospective study of the comparative frequency with which use of various antibiotics is followed by pseudomembranous enterocolitis has been done. The extensive literature in the 1950's implicating broad-spectrum antibiotics, especially tetracycline,[21,22,24,26,28] ceased until the last four years during which lincomycin and clindamycin have been strongly incriminated. Of the 42 patients with antibiotic-associated colitis reported since 1970 (Table 4), 26 received either lincomycin or clindamycin alone without other antibiotic therapy. Of all 42 patients, 38 received either lincomycin or clindamycin with only 4 patients given neither drug. Although the oral route of administration was more common, intramuscular

TABLE 4.—*Clinical Features and Role of Antibiotics (42 Total Cases)*

Underlying Illnesses: Wide spectrum from minor infections to major multisystems disease

Antibiotic	*Patients*
Antibiotics:	
Lincomycin alone	13
Clindamycin alone	13
Lincomycin or clindamycin plus other antibiotics	12
Neither lincomycin nor clindamycin	4
Interval from Initiation of Antibiotic Therapy to Diarrhea:	
Lincomycin	9 days (3 days to 3 weeks)
Clindamycin	7 days (1 day to 2 weeks)

Figure 4.—A segment of formalin-fixed colon from Case 1 shows the characteristic plaques with intervening normal-appearing mucosa. Some of the plaques are discrete, while others have become confluent.

or intravenous antibiotic therapy was also associated with the subsequent development of colitis with the majority of patients receiving low oral dosages. A recent prospective study documented pseudomembranous colitis in 10 percent of patients in hospital given clindamycin.[4] Although other currently used antibiotics such as tetracycline and ampicillin may be associated with pseudomembranous colitis,[5,10] the infrequency of these reports would suggest they seldom cause colitis. The interval from the initiation of therapy with lincomycin and clindamycin to the onset of diarrhea averaged nine and seven days, respectively, with a range from one day to three weeks (Table 4).

Lincomycin is a structurally unique antibiotic which has a spectrum similar to that of erythromycin.[29] It interferes with protein synthesis by inhibiting the binding of soluble ribonucleic acid to the ribosome-messenger complex in sensitive bacteria. The 7(S)-chloro substitution of the 7(R)-hydroxyl group of lincomycin resulted in a new semisynthetic antibiotic, clindamycin, which had greater in vitro activity and better intestinal absorption.[30] Whether the relation of these drugs to pseudomembranous colitis involves alteration of bowel flora or a direct toxic effect of the drug or one of its metabolites is not known.

Pathology

The pathologic findings of pseudomembranous enterocolitis are quite distinctive from other forms of colitis.[25] Although earlier descriptions of the pathology in the literature were similar, they were thought to be nonspecific because of the wide array of causes.[22-24] From the cases at our institution, four surgically resected segments of colon and two autopsy specimens of small intestine and remaining unresected colon were available for study. They showed similar gross and microscopic findings characteristic of pseudomembranous enterocolitis. Grossly the bowel was dilated and edematous. Numerous yellow-gray or yellow-green raised plaques, a few millimeters in diameter, were scattered over the mucosa of the entire colon. In some areas the lesions became confluent to form larger irregular placques (Figure 4). In the two autopsy specimens of more advanced enterocolitis, the pseudomembrane was confluent over a large portion of bowel. When the plaque was separated from the underlying mucosa, superficial ulceration was evident underneath. The mucosa between the plaques appeared relatively normal except for some edema. Only one of the four surgical specimens included a portion of distal ileum, which was uninvolved. The majority of the small intestine, however, was involved along with the remaining colon in the two autopsy specimens.

Microscopically, the plaques consisted of exudate composed of a mixture of fibrin and mucus in which a variable number of polymorphonuclear neutrophiles were present. Gram stains showed Gram-positive cocci in only one case. The goblet cells in the subjacent mucosa were increased in number and distended with mucus. The lamina propria of the mucosa showed an increased number of cells, but crypt abcesses were distinctly uncommon. The submucosa was congested and mildly edematous, but cellular infiltration was not a prominent feature. No vasculitis was present. The intervening mucosa was microscopically normal with the transition from involved to uninvolved areas being abrupt.

Therapy

Appropriate therapy for pseudomembranous enterocolitis has never been prospectively analyzed, but symptomatic therapy consisting of cessation of antibiotics, bowel rest and vigorous replacement of fluid and electrolytes losses (often huge) seems appropriate. Other supportive measures felt useful include oral lactobacilli,[6] fecal enemas,[7] and specific antistaphylococcus therapy if stool Gram stain indicates their presence.[18] The popularity of adrenocorticotropic hormone (ACTH) or steroids administered systemically or rectally is evidenced by Table 5 in which 47 percent (15 patients) of those patients whose therapy was stated received these drugs. It is also notable that 22 per-

TABLE 5.—*Therapeutic Measures and Mortality in Pseudomembranous Enterocolitis (42 Total Cases)*

Therapy	*Percent of Patients*
Symptomatic	100
Steroids or ACTH*	47
Operations	22

*Adrenocorticotropic hormone.

Outcome	*Patients*	*Percent of Known*
Survived	29	74
Died	10	26
Unknown	3	..

cent of patients whose therapy was stated required operations, usually subtotal colectomy. The indications included colonic perforation, toxic megacolon, suspected ischemic colitis, peritonitis and failure to respond to medical therapy. It is suspected by us and others[4] that early diagnosis and institution of supportive therapy with or without steroids would strikingly lower the frequency of complications, operations and mortality.

Outcome

Earlier reports listed mortality as high, usually 50 to 75 percent.[19] The mortality of the 39 patients in Table 5 whose outcome was stated was 26 percent. Clinical features related to death were not clear although adverse factors reported include delay in diagnosis,[24] confluent pseudomembrane[31] and seriousness of underlying illness.[7,18]

In conclusion, the available clinical information from 42 cases of antibiotic-associated colitis has been analyzed. It is hoped that these recent case reports describing lincomycin- and clindamycin-associated pseudomembranous colitis will stimulate studies to at least define the incidence of this colitis in all clinical settings and, moreover, to discover the mechanism by which antibiotic therapy leads to colitis. The incidence of enterocolitis associated with these antibiotics needs to be determined by careful prospective studies of various segments of the population. For now an awareness of the diagnostic features and therapeutic maneuvers may reduce morbidity and mortality of this formerly uncommon disease, apparently resurrected by modern antibiotic therapy.

Addendum

Since this paper was submitted for publication, more reports of antibiotic-associated colitis have been published. Cohen[32] described three additional patients with clindamycin-associated pseudomembranous colitis, one of whom died with toxic megacolon that developed at an unspecified time following examination using a barium enema. Abnormalities noted at barium enema were nonspecific and present in only half of all patients seen at their institution. Pittman[33] reported 16 patients with lincomycin-associated colitis that clinically and pathologically resembled ulcerative colitis. No pseudomembranes were present. The disease was mild with all patients recovering. Tedesco[34] extended his prospective study to 200 patients and still found a 10 percent incidence of clindamycin-associated colitis. In this setting of close surveillance, the disease was self-limiting without mortality following cessation of the antibiotic. The Upjohn Company sent a letter to all physicians on August 16, 1974 with current information regarding antibiotic-associated colitis implicating their products Cleocin® (clindamycin) and Lincocin® (lincomycin). Based on analysis of voluntary reports to their company of clindamycin-associated colitis and estimated patient drug usage, they suggest an incidence of 0.001 percent to 0.002 percent, strikingly lower than Tedesco's figure of 10 percent. More studies are needed to define true incidence.

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The History in Patients with Urinary Incontinence

There is little agreement among the experts on urinary incontinence. The only place where there is agreement is that most failures in the treatment of stress incontinence are not operative failures, but they are diagnostic failures. Of all the procedures used for evaluating urinary incontinence, the history is the easiest, one of the most important, and probably the most neglected. No special equipment is required, only time. It is necessary to ask all patients if they have urinary incontinence. Many little old ladies have had incontinence for years, but are embarrassed to mention it . . . or feel that it is women's lot in life and nothing can be done about it. Or possibly, they have talked to their next-door neighbor who was operated upon and is now worse. These operations have a bad name, despite the 95 to 100 percent cure rate quoted in the literature . . . The history is best taken by means of a form so that no questions are overlooked . . . When did your bladder difficulty start? (Patients with true stress incontinence practically always have a history of incontinence beginning with a pregnancy and becoming progressively worse with each pregnancy, only to improve following delivery. Incontinence returns, becoming severe at menopause.) What medications are you taking? (In our drug-oriented society, the list of medications that affect bladder function is growing at an astounding rate.) Do you have difficulty in starting your urinary stream? (This may represent an over-distended, thin-walled bladder or a urethral obstruction and the tense spastic patient may have these complaints, as it is impossible to urinate without relaxing the perineal muscles.) Do you notice dribbling of urine when you stand after urination? (This may represent a urethral stricture with a few drops of urine trapped behind it. It may represent a urethral diverticulum, but most commonly it is caused by a detrusor contraction secondary to an unstable or irritable bladder.) Do you feel that you completely empty your bladder? (If the patient says yes, this may or may not be true. But if the patient says no, she is invariably right.) Is urination painful after intercourse? (These patients usually have urethritis or possibly a urethral diverticulum. Most urinary tract infections in the female flare up secondary to intercourse.) Do you usually get up at night to urinate? (Nocturia two or more times indicates a small bladder capacity.) Does the sight, sound or feel of running water cause you to lose your urine? (Urinary incontinence associated with these sensations is typical of detrusor dysinertia.) Are you ever not aware that you are losing your urine? (Patients with detrusor dysinertia may have a continuous dribbling incontinence with no sensation of having to void.) Did you ever have to be catheterized because you were unable to urinate? (This is the experience of the patient with a partially decompensated bladder and overflow incontinence.) Do you find it necessary to wear some type of protection? (In my experience, incontinence of this degree is usually not stress incontinence. This may represent stress incontinence with superimposed urgency, or they have most likely some abnormality of bladder action.) While urinating, can you usually stop your stream? (The patient with true stress incontinence can do so. The patient with some abnormality of bladder action cannot. A detrusor contraction is set off and it cannot be stopped.) And finally, what do you think causes your bladder problem? (It is interesting that a number of patients say "Doctor, do you think it could be my nerves?" . . .)

—Jack R. Robertson, MD, *Los Angeles*

Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 21, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Specialty Conference

Participants

MELVIN M. SCHEINMAN, MD*
ROBERT PETERS, MD
DAVID S. HIRSCHFELD, MD
JOSEPH A. ABBOTT, MD†
FRED KUNKEL, MD

Refer to: Scheinman MM, Peters R, Hirschfeld DS, et al: The sick sinus and ailing atrium—Teaching Conference, San Francisco General Hospital and University of California, San Francisco (Specialty Conference). West J Med 121:473-481, Dec 1974

The Sick Sinus and Ailing Atrium

ROBERT PETERS, MD:‡ The human sinus node is a small ovoid structure located at the junction of the superior vena cava and right atrium. The artery to the sinus node courses through the center of the node and the node has aptly been described as an "enormous adventitia" of the artery.[1] The node itself is composed of a dense collagenous framework that is attached to the central artery and clusters of interlacing fibers.[2] The fibers contain predominately two types of cells—cells with large ovoid nuclei and few myofibrils (P cells) and cells intermediate in histologic structure between P cells and atrial myocardial cells. The sinus node tracts merge, especially at the periphery of the node, and form large Purkinje-like tracts that course through the atrial myocardium. The P cells are thought to be the site of impulse generation, while the perinodal fibers probably serve to amplify and synchronize the impulses arising from the sinus node cells.[3]

Normally, the sinus node is the dominant cardiac pacemaker because its discharge rate is more rapid than the other automatically discharging cells within the heart. Because the sinus node discharge rate must ordinarily vary greatly to meet body needs, it is not surprising to find that it is richly innervated by postganglionic sympathetic and parasympathetic fibers.

Disease of the sinus node may become manifest by abnormalities in impulse generation and/or impairment of impulse conduction through the sinoatrial junction. Relatively few detailed histologic studies are available for patients with sinus node dysfunction. These studies[4-7] and other electrophysiologic studies[8,9] would suggest that these patients commonly have disease not only of the sinus node but also of the approaches to the sinus node, the atrium, the atrioventricular (A-V) node, and the ventricular specialized conduction system.

We have divided this discussion into four sections. Dr. Hirschfeld will explore the clinical and electrocardiographic features, Dr. Abbott will discuss the importance of exercise stress testing, Dr. Kunkel will describe the electrophysiologic testing and Dr. Scheinman will conclude by discussing the management of patients with sinus node disease.

Clinical and Electrocardiographic Features

DAVID S. HIRSCHFELD, MD:§ Twenty-eight patients with symptoms and electrocardiographic evidence of sinus node dysfunction were observed for a

From the Medical Service, San Francisco General Hospital, and the Department of Medicine and the Cardiovascular Research Institute, University of California, San Francisco.

Supported in part by Grant HL 06285, National Institutes of Health, Bethesda, Maryland.

*This study was performed during tenure of the American Heart Association Teaching Scholar in Cardiology.

†Supported in part by Alfred Stengel Traveling Scholarship of the American College of Physicians.

‡Clinical Instructor in Medicine, University of California, San Francisco; member of staff, San Francisco General Hospital.

Reprint requests to: M. M. Scheinman, MD, Medical Service, San Francisco General Hospital, 1001 Potrero, San Francisco, CA 94110.

§Cardiology Fellow, University of California, San Francisco, School of Medicine; Medical Service, San Francisco General Hospital.

TABLE 1.—*Clinical Spectrum of Patients with Sinus Node Disease*

Symptoms and Cardiovascular Diagnosis	*Number of Patients*			
	Sinus Bradycardia	*Bradycardia-Tachycardia Syndrome*	*Sinus Arrest*	*Total*
Number in group	13	11	4	28
Syncope	8	4	4	16
Near syncope	1	3	0	4
Angina	3	1	0	4
Palpitations	0	4	0	4
Conduction defect*	4	4	1	9
Congestive heart failure	5	5	1	11
Hypertension	6	1	0	7
Previous history of myocardial infarction	3	3	0	6
Cerebrovascular accident	3	0	0	3
Cardiac amyloidosis	0	2	0	2

*Either PR prolongation or bundle branch block or hemiblock pattern.

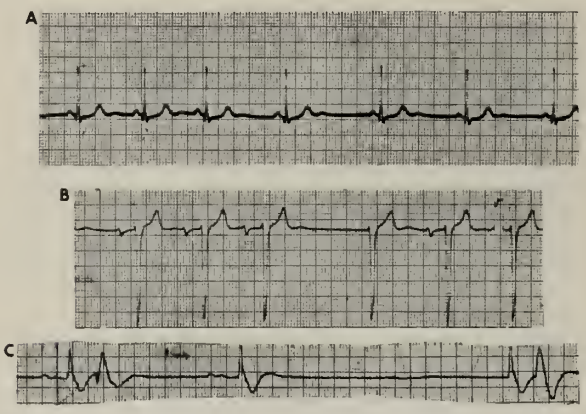

Figure 1.—Representative electrocardiograms from patients with symptomatic sinus bradycardia (Group I). **A**, after the third complex, there is abrupt slowing of the sinus rate. **B**, sinus exit block. Three sinus beats are followed by a pause that equals 3 P-P intervals. The fourth QRS complex is an escape junctional beat. **C**, the first and third complexes are sinus beats, after which a sinus pause of 3½ seconds is terminated by a junctional escape beat.

mean period of 18 months. All of them underwent prolonged continuous electrocardiographic monitoring either in a coronary care unit or by means of a continuous tape memory loop (Holter) system. Only patients with chronic rhythm disturbances were included, and patients with sinus bradycardia that may have been related to drugs, electrolyte imbalance, thyroid dysfunction or acute myocardial infarction were excluded from this study.

The mean age for the group as a whole was 54±19 years and the range was from 10 to 80 years. The age distribution appeared to be bimodal with one peak at a mean age of 31 and a second peak at 63 years. Sixteen men, one boy, and eleven women were studied. The group was further subdivided into three subgroups on the basis of the major cardiac rhythm disturbance found (Table 1). Group I consisted of 13 patients with sinus bradycardia that was defined as a persistent resting heart rate below 55 beats per minute. Electrocardiographic rhythm strips in 11 patients (Group II) showed alternating sinus bradycardia and tachycardia. Finally, electrocardiograms of four patients (Group III) showed periods of sinus arrest, defined as cessation of all atrial activity associated with cardiac asystole for at least 5 seconds. Although each patient was assigned to a group on the basis of the predominant rhythm disturbance found, considerable overlap in the type of arrhythmias was observed among patients in the three groups. The pertinent clinical data are summarized in Table 1.

Near syncope or syncope was the most common symptom (9 of 13 patients) for patients with symptomatic sinus bradycardia (Group I). The most common rhythm disturbance for patients in this group (and in Groups II and III) consisted of episodic sinus slowing—with or without evidence of sinus node exit block—(Figure 1A and B). The sinus slowing was often followed by escape junctional or ventricular beats (Figure 1C). Only one patient in this group required a permanent intracardiac pacemaker for control of heart failure. In the remaining patients in this group symptoms of left-sided cardiac failure were well controlled with digitalis and diuretic therapy.

Supraventricular arrhythmia including paroxysmal atrial or junctional tachycardia and atrial fibrillation or flutter was observed in ten patients with bradycardia-tachycardia syndrome (Group II). One patient with multiple myeloma and persistent sinus bradycardia (alternating with a slow

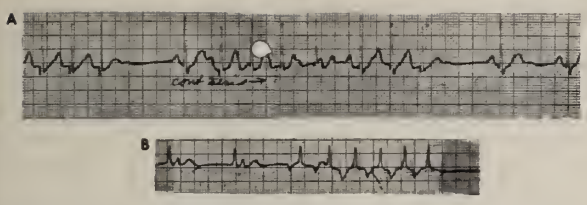

Figure 2.—Representative electrocardiograms from patients with supraventricular arrhythmias (Group II). **A,** an episode of paroxysmal atrial tachycardia terminates spontaneously. After a sinus beat (fourth complex), atrial tachycardia with Mobitz I atrioventricular block resumes. **B,** a junctional rhythm is interrupted by an episode of paroxysmal atrial tachycardia (third complex).

junctional rhythm) had recurrent bouts of ventricular tachycardia requiring electroconversion. The onset of the tachycardia was recorded in six patients, and in all recorded instances the tachyarrhythmia was initiated by a premature supraventricular beat and never observed to begin after a prolonged sinus pause. Two examples of this phenomenon are illustrated in Figure 2. Bouts of supraventricular arrhythmia were often followed by a prolonged pause terminated by atrial or junctional escape beats. On follow-up, stable atrial fibrillation developed in one patient and it was well controlled with digitalis therapy. Three patients required insertion of a permanent right ventricular pacemaker for control of severe symptomatic sinus bradycardia, recurrent ventricular tachycardia, or Stokes-Adams attacks resulting from 3° A-V block. The patient with multiple myeloma died because of repeated pulmonary embolization.

One patient in the group with sinus arrest (Group III) had recurrent syncopal episodes and cardiac arrest owing to sinus arrest, and cardiac asystole was documented on two occasions (Figure 1C). This patient, however, had a regular sinus rhythm and normal heart rate during prolonged repeated monitoring in a coronary care unit and during a 12-hour Holter recording. One patient had persistent sinus bradycardia, and the remaining two patients had alternating sinus bradycardia, supraventricular tachycardia, and cardiac arrest owing to sinus arrest and cardiac asystole. The four patients in this group all required permanent intracardiac pacemakers. Of particular interest was one patient in this group who continues to have symptoms of presyncope even after insertion of a normally functioning demand right ventricular pacemaker.

Several clinical features of this disease entity deserve emphasis. Contrary to prevailing belief, sinus node dysfunction is not limited to the elderly;[5,10] our youngest patient, for example, was ten years of age, and one-third of our subjects were less than 50. Although coronary artery and hypertensive cardiovascular diseases are commonly associated conditions[10-12] (Table 1), the paucity of detailed histologic studies makes a causal link rather tenuous. Clinical,[5,8,10,11,13] electrophysiologic,[14] and histologic[4] studies have conclusively demonstrated associated disease of both the A-V node and the ventricular specialized conducting system in many patients with sinus node disease. This finding has important therapeutic implications with regard to the site of pacemaker implantation. Finally, although the natural history of this disease is still unclear,[15] there appears to be wide variability in severity of symptoms and progression of disease. Fortunately, deaths due to arrhythmia appear to be uncommon.[5,10,13]

In summary, most patients with sinus node disease may be diagnosed by scrutiny of electrocardiographic rhythm strips. In our experience, the most common finding is persistent sinus bradycardia, oftentimes associated with periods of gradual further slowing of the sinus rate and escape of a lower pacemaker. Some patients also show cardiac arrest resulting from sinus arrest and cardiac asystole, while others show an alternating bradycardia-tachycardia arrhythmia.

Exercise Stress Testing

JOSEPH A. ABBOTT, MD:* Syncope, tachyarrhythmia, and cardiac arrest are well known manifestations of the sick sinus syndrome.[16] Because of the advanced age of many patients with the sick sinus syndrome and the tendency of the elderly to lead less physically active lives the effort-induced disabilities these subjects suffer are less well appreciated.[17,18] We performed both autonomic screening and exercise tests in nine control subjects and 15 of the patients previously described by Dr. Hirschfeld. Most were young and physically active and were without clinical evidence of myocardial disease. Both the exercise and autonomic studies were thoroughly explained and an informed consent statement was signed by each patient and control.

Nine male and six female patients with the sick sinus syndrome, ranging in age from 10 to 77 years (mean 47 years), and nine control subjects were

*Associate Clinical Professor of Medicine, University of California, San Francisco, School of Medicine; Assistant Director, Cardiopulmonary Unit, San Francisco General Hospital.

exercised on a bicycle ergometer,* using a technique that allows serial measurement of heart rate and oxygen consumption at incremental levels of exercise.[19] The study groups included patients in each of the three previously described categories: five patients in Group I, six patients in Group II, and four patients in Group III. Five patients had functioning permanent demand ventricular pacemakers at the time of the study. Patients who were poorly motivated, had orthopedic limitations, severe lung disease, unstable angina, or a recent myocardial infarction were excluded from exercise evaluation. Control subjects were matched as to sex and age with the study group and included staff physicians, medical interns and residents, and laboratory technicians. Exercise was stopped when patients expressed a desire by signaling the physician or when they developed objective evidence of untoward cerebral or cardiac symptoms—lightheadedness, breathlessness, arrhythmia, or fainting. No untoward effects were noted in control subjects and effort was terminated when 90 percent of the age-predicted maximum heart rate was achieved.

Since dysfunction of the autonomic system may be present in patients with the sick sinus syndrome, autonomic screening tests including the Valsalva maneuver, carotid sinus massage, and measurement of blood pressure and heart rate in supine and upright positions were performed before the exercise tests.[15,20-23] After a 15-minute recovery period from exercise, 1.0 mg of atropine sulfate was administered intravenously over a 5-minute period during which the heart rate was recorded.[24]

The resting heart rates of the patients in Group I (46±6 beats per minute) and Group II (50±10 beats per minute) were significantly below the resting heart rates of control subjects (78±10 beats per minute) or patients in Group III (72±11 beats per minute) in whom ventricular demand pacemakers were set at rates of approximately 70 beats per minute. With exercise, patients with sinus node disease were unable to achieve heart rates comparable to those in control subjects (Chart 1). The differences were statistically significant ($p<0.05$), even though the normal subjects were only stressed to 90 percent of their maximum predicted heart rate. Mean resting oxygen consumption was similar in control

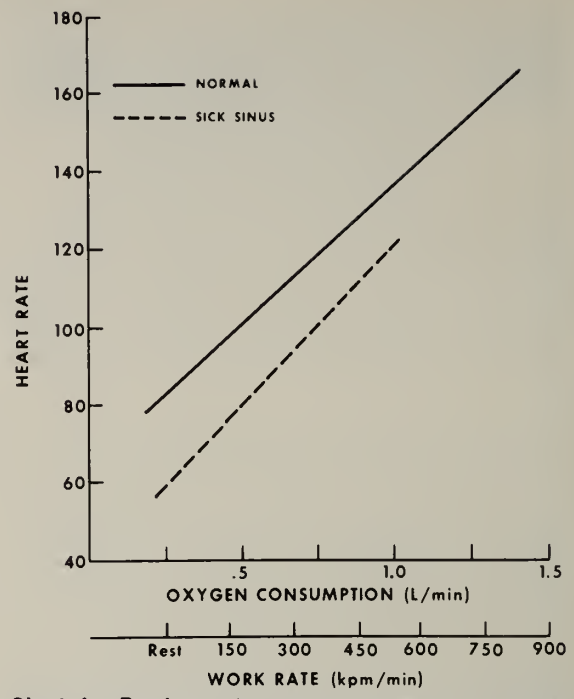

Chart 1.—Resting and maximal exercise oxygen uptake and work rates are plotted against heart rate. The curve of the 15 patients with sinus node disease lies to the right of the curve for control subjects. Both heart rate response and the work performance level (maximal oxygen uptake) are blunted in patients with sinus node disease.

(0.195±0.05 liters per minute) and patients (0.210±0.08 liters per minute) groups. Mean oxygen consumption at maximum stress (Chart 1) was significantly lower for patients (1.01±0.18 liters per minute) compared with predicted maximum oxygen consumption for control subjects (1.65±0.31 liters per minute) ($p<0.005$). Similarly, work levels achieved at the termination of exercise were significantly lower for patients (mean 450 kg-meters per minute) than for control subjects (mean 900 kg-meters per minute) ($p<0.05$). Six of the patients had permanent or temporary demand ventricular pacemakers inserted to prevent syncope or to treat symptoms of heart failure. In each the pacemaker rate had been set between 65 and 70 beats per minute. When exercise performance of these patients was compared with that of the subgroup of patients without pacemakers, there was no significant difference in maximum exercise oxygen uptake and none of the patients with ventricular pacemakers had relief from their exercise-induced symptoms. The reason for termination of exercise was dizziness, which was often related to cardiac arrhythmia, to development or worsening of symptoms of con-

*Bicycle ergometer Model AM368, Elema Schonander, Stockholm, Sweden.

TABLE 2.—*Exercise-Induced Signs and Symptoms in Patients with Sinus Node Disease*

	Number of Patients with Signs and Symptoms					
Group Number	*Development or Worsening of Heart Failure*	*Fatigue*	*Angina*	*Faint*	*Dizzy*	*Arrhythmias Noted*
I	2	1	1	1	0	0
II	0	1	0	0	4	Atrial flutter Ventricular tachyarrhythmia Atrial fibrillation
III	1	2	0	0	2	0

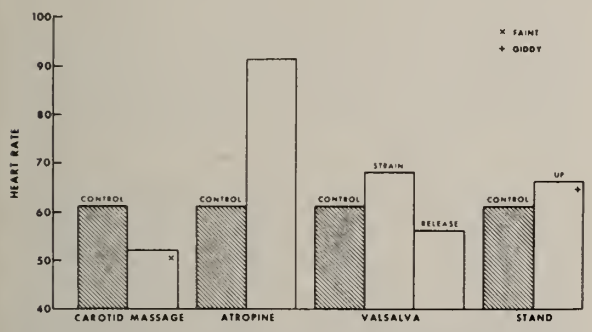

Chart 2.—The heart rate responses to autonomic screening are charted in 15 patients with the sick sinus syndrome. The heart rate responses are qualitatively normal for each test maneuver. However, the changes in heart rate were less than those observed for the normal subjects. In three instances abnormal responses were associated with cerebral symptoms (faintness with carotid massage in two instances and giddiness with hypotension on tilting in one).

gestive heart failure, exhaustion, or angina; exercise-induced arrhythmias were noted only in the patients in Group II. These findings are detailed in Table 2.

Patients with sick sinus disease clearly show abnormal exercise stress performance.[25,26] This finding may be owing to several factors:[27] the patients may have been in poor physical condition, had impaired myocardial function or autonomic dysfunction or both, or had end organ (sinus node) disease. Any or all of these alternatives could prevent the normal acceleration of the sinus node rate to meet body needs. Subjects in poor physical condition show an increased heart rate for any given level of exercise; our patients had heart rates lower than control subjects for each exercise load. Exercise performance in the control group, in fact, fell into an "unfit" category.[28] Thus, the differences in work performance between the patients and the control subjects were not owing to differences in physical conditioning. Although 10 of 15 patients (67 percent) had no clinical evidence of cardiac disease, the inability of the patients to achieve maximum oxygen consumption and work rate levels may well have resulted from an inability to increase stroke volume to compensate for a blunted increment in exercise heart rate.[29]

Autonomic screening is an important part of the evaluation of the patient with sick sinus disease. In our study the screening procedures used involved those tests that could readily be performed at the bedside, including carotid massage, Valsalva's maneuver, tilting, and electrocardiographic monitoring before and after intravenous injection of atropine sulfate.[30] The effects of these procedures are summarized in Chart 2. In brief, these patients showed a somewhat blunted but qualitatively normal response in heart rate and blood pressure. In two patients carotid sinus massage led to an inordinate slowing of the heart rate and a fall in blood pressure and was associated with near syncopal symptoms. Another patient, a 60-year-old diabetic woman who required a permanent demand ventricular pacemaker to prevent recurrent cardiac asystole owing to sinus arrest, first presented with fainting spells, and pacemaker malfunction was suspected. Subsequent complete autonomic testing revealed a mixed parasympathetic and sympathetic disorder. Her symptoms of recurrent cardiac arrest resulted from sick sinus disease, which had been adequately managed by a demand ventricular pacemaker. Her autonomic disorder was responsible for her postpacemaker "drop attacks" and mimicked pacemaker malfunction.

In summary, physiologic stress testing and autonomic screening procedures may be of great clinical value in the evaluation of patients with symptomatic sinus node disease. Primarily, serious arrhythmias may be uncovered by exercise stress testing, which may lead the clinician to institute specific antiarrhythmic therapy or suggest limitation of strenuous activities. In addition, while pacemaker therapy is eminently successful in the

prevention of bradyarrhythmias and syncope, our studies clearly show that such therapy is ineffective in abolishing exercise-induced symptoms; thus, patients who are young and active should properly be forewarned before insertion of a pacemaker. Finally, since autonomic disease may mimic or exacerbate symptoms in patients thought to have sinus node disease, careful evaluation of the autonomic nervous system is essential; autonomic dysfunction may require additional therapeutic management.

Electrophysiologic Testing

FRED KUNKEL, MD:* Various electrophysiologic abnormalities have been found in patients with sinus node disease. Abnormal prolongation of postpacing depression of sinus node automaticity (sinus node recovery time) commonly occurs in patients with sinus node dysfunction.[15] This test is thought to test the generator function of the sinus node.[31] Strauss et al[32] suggested use of coupled electrically induced atrial depolarizations to measure sinoatrial conduction time. Coupled atrial beats (A_1A_2†) induced late in the atrial cycle (that is, greater than 75 percent of the spontaneous cycle length, A_1A_1†) result in progressive linear prolongation of the subsequent return cycle (A_2A_3†). This has been designated as Zone I by Strauss and his colleagues.[32] During Zone I, the sinus node is not depolarized or "reset," and the test cycle (A_1A_2) plus the subsequent return cycle (A_2A_3) is equal to twice the spontaneous cycle length (A_1A_1). Progressively earlier coupled atrial depolarizations, however, result in return cycles of similar length (Zone II), which is ascribed to premature depolarization or "resetting" of the sinus node. In Zone II, since the sinus node is reset, A_1A_2 plus A_2A_3 is less than twice A_1A_1. The difference between A_2A_3 and A_1A_1 during Zone II and hence the point in the A_1A_1 cycle at which Zone I changes to Zone II has been suggested as another index of sinoatrial conduction time. Therefore, if the conduction time into the sinus node were prolonged, Zone I would constitute a greater proportion of the return cycle and A_2A_3 during Zone II would be abnormally lengthened. Strauss and coworkers[32] found one patient with sinus node disease who never reached Zone II, and they defined this phenomenon as 1° sinus node entrance block. In our studies we measured the effective atrial refractory period in addition to the tests just described. The effective refractory period of the atrium is defined as the shortest interval between the spontaneous (or driven atrial beat) atrial depolarization and the coupled electrical impulse that results in atrial depolarization.[33]

Twenty-one of our 28 patients underwent these electrophysiologic tests in order to better define sinus node and atrial function as well as to measure atrioventricular conduction times. In addition, 15 control subjects without any evidence of sinus node dysfunction (who were referred to our laboratory for atrial pacing as part of their evaluation for chest pain) were also studied. Informal written consent, according to a protocol approved by the University Committee on Human Experimentation, was obtained from each patient before the study. A quadripolar electrode catheter was inserted against the high lateral right atrial wall for purposes of atrial pacing. An additional electrode catheter was inserted into a femoral vein and positioned across the tricuspid valve for recording the His bundle deflection.[34] Sinus node recovery times were obtained after abruptly terminating atrial pacing at rates of 100 and 120 beats per minute. The atrial cycle was then scanned (as described) by means of single electrically induced coupled atrial depolarizations at various intervals after spontaneous atrial depolarizations. Finally, the effective atrial period was determined at varying paced atrial rates.

The sinus node recovery time (interval from last paced atrial beat to the next spontaneous atrial depolarization) was prolonged in 16 of the 21 patients (Chart 3). The longest sinus node recovery time in the control group was 1,230 msec. The results of atrial scanning are summarized in Chart 4. Simultaneous plots of test (A_1A_2) versus return (A_2A_3) cycles showed three types of curves. The "normal" curve shown in the cross-hatched area shows both Zones I and II as described previously. Zone II was reached at a mean A_1A_2 interval of approximately 80 percent of the control cycle length. Two patients with sinus node disease showed abnormal curves (one of these patients had a normal sinus node recovery time): in one, Zone II was never achieved (1° sinus node entrance block), and in the other, Zone II was achieved at A_1A_2 intervals of less than 50 percent of the spontaneous cycle length. Five of the 21

*Research Fellow, Cardiovascular Research Institute, University of California, San Francisco.

†A_1A_1 = spontaneous cycle length, A_1A_2 = interval from spontaneous atrial beat to coupled atrial depolarization, and A_2A_3 = interval from induced atrial premature beat to the next spontaneous atrial beat.

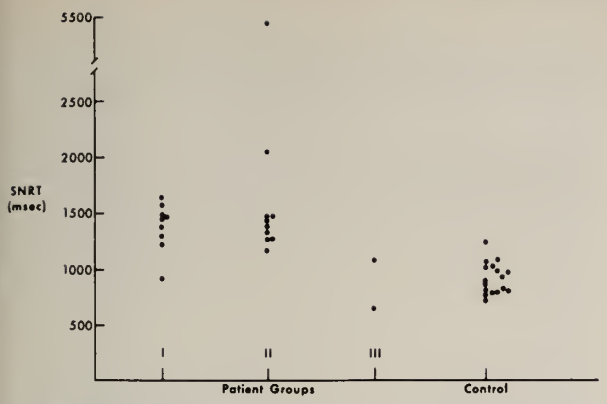

Chart 3.—Sinus node recovery times (SNRT) for the three groups of patients with sinus node disease and for control subjects following atrial pacing at 100 beats per minute. Sixteen of 21 patients with sinus node disease showed abnormally prolonged SNRT.

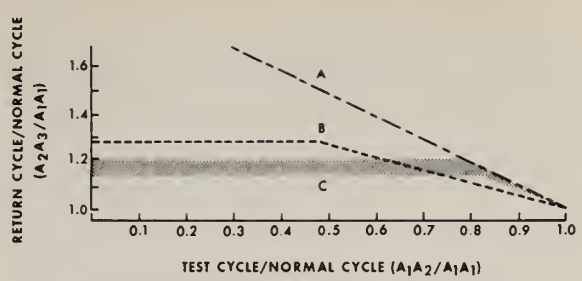

Chart 4.—Relationship between test (A_1A_2) and return cycles (A_2A_3). The numbers 1.0 on the ordinate and abscissa, through which lines are drawn, represent the corrected spontaneous atrial cycle length of each person tested ($A_1A_1/A_1A_1=1.0$). Points along the abscissa represent fractions (in tenths) of A_1A_1 at which premature atrial beats were placed (test cycle on A_1A_2). For each A_1A_2 interval, the recovery cycle (A_2A_3) was also recorded and expressed as a fraction (in tenths) of A_1A_1. Thus, recording the corrected recovery time (A_2A_3/A_1A_1) for every corrected test cycle (A_1A_2/A_1A_1) allows for direct comparison of patients with different cycle lengths. Cumulative points of test (A_1A_2) and return cycles (A_2A_3) for all subjects are shown. A and B are the two abnormal curves and C is the composite "normal" curve points.

patients showed abnormal prolongation of the atrial effective refractory period (even when corrected for cycle length);[35] however, all five showed prolonged sinus node recovery time. One patient with a persistent slow junctional rhythm showed no spontaneous atrial depolarization or contraction (by fluoroscopy), and the atrium was inexcitable despite repeated attempts to pace from different positions in the right atrium with maximum current flow of 25 milliamperes.

The study design allowed for evaluation of both sinus node and atrial function as well as A-V nodal and infranodal conduction. Abnormalities in A-V nodal conduction as determined by prolongation of the interval from the low right atrial electrogram to the His deflection[36] or by A-V nodal block induced by atrial pacing was found in six patients with sinus node disease. Prolongation of infranodal conduction (interval from His deflection to the onset of ventricular activation)[36] was found in five.

In summary, electrophysiologic testing is important in both substantiating the diagnosis of patients with sinus node dysfunction and in determining the site for pacemaker implantation. Seventeen of the 21 patients showed some abnormality in generator function, sinoatrial conduction, or atrial refractoriness. Clearly, the most sensitive and specific test was the sinus node recovery time, which was abnormally prolonged in 16 of the 21 patients with sinus node disease. Normal sinus node recovery time may occur in patients with sinus node disease, presumably because of the block of entry of driven atrial beats into the sinus node.[32] Two patients showed abnormalities in sinoatrial conduction, and one of these patients had normal sinus node recovery time; one patient showed atrial inexcitability. Likewise, a significant number of patients with sinus node disease (45 percent) showed abnormalities in A-V conduction. If permanent pacemaker insertion is necessary, then obviously a ventricular rather than an atrial pacemaker is indicated for patients showing significant abnormalities in A-V conduction.

Management of Patients

MELVIN M. SCHEINMAN, MD:* The wide variability in both symptoms and courses of patients with sinus node disease necessitates careful individualization of both the evaluative testing just described and the therapy. In patients with sinus bradycardia or sinus arrest or both, associated with recurrent bouts of syncope, intracardiac pacemaker therapy is clearly indicated.[12] Rationale for the different types of pacemakers employed will be discussed later. Quite clearly, drug therapy (isoproterenol or belladonna derivatives) is ineffective for long term control of these cardiac arrhythmias;[16] however, digitalis may be used to control symptoms of congestive heart failure in patients with sinus bradycardia.[10] On the other hand, many patients will present with electrocardiographic findings of sinus bradycardia and a history of episodic symptoms (for example, giddiness, syncope, angina). For these patients prolonged electrocardio-

*Associate Professor of Medicine, University of California, San Francisco, School of Medicine; Chief, Coronary Care Unit, San Francisco General Hospital.

graphic taped (Holter) monitoring may prove invaluable in detecting episodic severe sinus slowing or arrest associated with the symptoms or both. If prolonged electrocardiographic monitoring fails to reveal sinus slowing or arrest, then the evaluative tests described herein may be quite helpful in detecting sinus node dysfunction. Our experience suggests that an integrative approach utilizing tests to evaluate the autonomic nervous system, exercise stress testing, and studies of the sinus node recovery time, sinus node conduction time, and atrial refractoriness may help distinguish patients with sinus node dysfunction from patients with sinus bradycardia resulting from hypervagotonia. In general, patients with sinus node disease show a blunted response as to changes in heart rate after atropine administration as well as the Valsalva or upright tilt procedures and exercise. Persons with hypervagotonia, however, show a brisk increase in heart rate after administration of atropine and a normal increase in heart rate and cardiac output during exercise stress testing.[20] Finally, the vast majority of our patients showed abnormalities in electrophysiologic stress testing designed to evaluate sinus node generator function, sinoatrial conduction time, or atrial refractoriness, or both. The finding of one or more abnormalities on testing does not necessarily dictate the need for insertion of a permanent intracardiac pacemaker; rather, this decision is made on the basis of the seriousness of the patient's symptoms. It is well appreciated that the symptom-free interval may last for many years,[10,16] and, furthermore, symptoms may be relatively minor (episodic fatigue, giddiness) and well tolerated. In our view, only patients with documented sinus node disease and at least one clear-cut syncopal episode should undergo insertion of a permanent intracardiac pacemaker.

Patients with the bradycardia-tachycardia syndrome may be symptomatic because of either pronounced sinus slowing or arrest or rapid supraventricular arrhythmias. In the latter group, digitalis is the mainstay of therapy. Others, however, have reported further sinus node slowing after digitalis[25,37] therapy. The use of suppressants (quinidine, procaine amide, and propropanolol [Inderal®]) should be used with caution since they may result in further severe slowing of the sinus rate.[10,38] We believe that exercise stress testing (especially in young patients) is of value in uncovering serious cardiac arrhythmia, and it may suggest either restrictions of extreme exercise or more aggressive medical treatment or both. Pacemaker therapy has greatly simplified management of these patients in that the bradycardia is controlled and digitalis or suppressants or both may be used for control of supraventricular arrhythmias. In our experience, the supraventricular tachyarrhythmias in these patients were usually initiated by a premature atrial discharge (rather than escape of another supraventricular focus). Similarly, electrically induced coupled atrial premature beats regularly initiated supraventricular tachycardia in two patients in this group with evidence suggesting a sinus node reentrant arrhythmia[39] in one and A-V node reentry in the other.[40] The widespread pathologic changes already alluded to appear to present the proper milieu for these reentrant arrhythmias. Atrial overdrive pacing (or ventricular pacing with 1:1 retrograde A-V conduction) may be sufficient to prevent the supraventricular tachyarrhythmias.

Atrial demand pacemakers have the advantage over other pacemakers of preserving the normal "atrial booster" mechanism, which may be particularly important in patients with congestive heart failure. In addition, atrial overdrive may prevent supraventricular tachyarrhythmias in patients with the bradycardia-tachycardia syndrome. On the other hand, consistent pacing from either the atrium or coronary sinus may be impossible using the transvenous route of catheter insertion and may require thoracotomy with insertion of the electrodes into the atrial myocardium. Pervenous permanent right ventricular pacing is favored because of ease of catheter insertion and because the patient is protected should A-V block eventually develop. His bundle recordings and atrial pacing are quite helpful in detecting patients with associated impairment of A-V conduction who clearly require a ventricular pacemaker. Right ventricular pacing does, however, produce asynchrony between atrial and ventricular contraction, which may result in diminished cardiac output.[41] In addition, if retrograde ventriculoatrial conduction is intact, conceivably retrograde atrial impulses may trigger bouts of supraventricular arrhythmias[39,40] as discussed previously.

Finally, an experimental bifocal electrode demand pacemaker with one pacemaker positioned in the right atrium and the second in the right ventricle is also available. When sinus slowing is associated with A-V block, both atrium and ventricle are paced in sequence. This pacemaker system has been employed successfully in a relatively small number of patients with sinus node disease.[42]

Insertion of a temporary transvenous cardiac pacemaker is recommended before insertion of the permanent pacemaker to allow for a smoother intraoperative course. In addition, when appropriate, the patient may be exercised with the temporary pacemaker in place at varying paced rates to determine the rate that results in optimal cardiac performance.

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Refer to: Dissecting aneurysm—Medical Staff Conference, University of California, San Francisco. West J Med 121:482-489, Dec 1974

Dissecting Aneurysm

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *As all of you know, one academic year has drawn to a close and another is just beginning as the cycle renews itself. We just this week greeted the new group of medical interns who will be starting with us, and very shortly the new residents will begin this cycle. I think you are all aware, as well, that much of the excitement and performance of our program is dependent upon the superb quality of the house staff with whom we are privileged to work in this institution. At the very top of the house staff sequence are the chief residents who stand in a somewhat ambiguous position between the proletariat of the house staff and the establishment of the faculty. They are amphoteric in their function, part teacher and part member of the house staff. We have been particularly fortunate this year in having two chief residents who have performed brilliantly in this capacity. It has been traditional for the chief residents to give the last Grand Rounds of the year and that tradition will be maintained today. The first topic will be that of dissecting aneurysm and John Stoner will be the speaker. We appreciate the leadership which he has brought to our program in this last year.*

DR. STONER:† The patient for discussion this morning is a 69-year-old retired Dutch pastry chef who was in good health until ten years before admission when hypertension was first noted and treated with hydrochlorothiazide and methyldopa, maintaining the blood pressure in the range of 140/80 to 160/100 mm of mercury. Over the succeeding five to six years the patient had several admissions to the hospital to rule out myocardial infarctions. Each time he would present with cramping anterior chest pain with radiation to the arm and neck. On these occasions he was noted to have a systolic crescendo-decrescendo murmur radiating to the neck. Chest x-ray films showed a tortuous ectatic aorta and electrocardiograms showed ST segment depression in the lateral precordial leads, but no findings that were thought to indicate an acute myocardial infarction. This was followed by a relatively symptom-free period until four months before admission when the patient developed abdominal pain with radiation to the back. On laparotomy, a perforated sigmoid diverticulum was noted which was treated by hemicolectomy. The patient then remained well until the day of admission when he presented to the emergency room with a sudden onset of intense substernal chest pain which radiated through to the back. Pertinent past history included long-standing nephrolithiasis and nephrocalcinosis. On subsequent physical examination, there was a blood pressure of 230/130 mm of mercury in both upper extremities, a pulse rate of 95, respiratory rate of 16 and a temperature of 37°C (98.6°F). His

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†John R. Stoner, MD, Chief Resident in Medicine.

Figure 1.—Initial chest x-ray film.

Figure 2.—Aortogram showing a large dissecting aneurysm.

chest was clear to auscultation and percussion. On examination of the heart, a left ventricular thrust was noted. The point of maximal impulse was at the anterior axillary line. A grade III/VI systolic crescendo-decrescendo murmur was heard at the left sternal border with radiation to the base and neck. Arterial pulses were equal bilaterally throughout and bruits were heard over the left subclavian and left femoral arteries. The serum creatinine level was 1.9 mg per 100 ml and there was microscopic hematuria.

The initial chest x-ray study showed a widening of the mediastinum when compared with previous studies (Figure 1). The electrocardiogram was unchanged from the earlier tracings. The creatine phosphokinase (CPK) and lactic acid dehydrogenase (LDH) isoenzymes were within normal limits. The patient's blood pressure was lowered to 120/80 mm of mercury by the use of a trimethaphan intravenous drip. Aortography using the Seldinger technique was then done. This showed a dissecting aneurysm which originated just distal to the left subclavian artery and extended below the diaphragm to involve the abdominal aorta (Figures 2 and 3).

Following angiography, the patient was continued on trimethaphan and methyldopa was begun. The blood pressure remained well controlled and the patient's pain was relieved. Twelve hours after admission, however, the patient's chest pain recurred with radiation to the back. The blood pressure fell to 40 systolic and the central venous pressure was found to be 7 cm of water. A chest x-ray film showed evidence of a left pleural effusion (Figure 4) and thoracentesis was done with return of bloody fluid. The patient was then given numerous transfusions followed by emergency thoracotomy with resection of the descending thoracic aorta distal to the left subclavian artery and replacement by a dacron graft.

Following an initial recovery, the patient again became hypotensive 24 hours after admission and subsequently died. At autopsy, further dissection and rupture of the abdominal aorta was found. On histological sectioning, cystic medionecrosis was noted.

This patient presented many of the typical findings that are seen with dissecting aortic aneurysm: a long-standing history of hypertension, pronounced elevation of the blood pressure at the time of presentation and rather characteristic chest pain which began anteriorly with radiation through to the back. The pain was sudden in onset and intense in character. In spite of the poor outcome, the diagnostic and therapeutic approach to this case was appropriate.

Figure 3.—Aortogram showing extension of the aneurysm below the diaphragm.

Figure 4.—Chest x-ray film showing a left pleural effusion.

Dissecting aneurysm or hematoma of the aorta has been defined as the penetration of blood into the aortic wall with extension for a variable distance along its length and circumference.[1] As an entity it was first described over 200 years ago with one of the earliest reported cases being that of King George II of England. The diagnosis, however, was not made antemortem with any consistency until the past 15 or 20 years with the more widespread recognition of its signs and symptoms and the advent of modern angiography, which allowed confirmation of the diagnosis before death. With the recent development of effective medical and surgical therapy, the early diagnosis of dissecting aneurysm and the institution of appropriate treatment has become critical.

Though uncommon, aortic dissection is by no means rare. It was found to have an incidence of one per 363 autopsies among a compilation of 31 published series.[1] In a report from this institution by Mote and Carr in 1942, there was a 1.1 percent incidence of dissecting aortic aneurysm among autopsies performed at the San Francisco Coroner's Office in cases of unexplained sudden deaths.[2]

With regard to pathogenesis, the vast majority of patients with dissecting aneurysm are found histologically to have some form of medial degeneration. In a series of 212 cases,[1] 62 percent were found to have Erdheim's cystic medionecrosis characterized by the accumulation of mucopolysaccharide in the media with loss of muscle and elastic fibers and the formation of cystic spaces. In the series, 17 percent were found to have other types of medial degeneration and only 16 percent were felt to be normal.

Conditions that predispose to the development of dissecting aneurysm include Marfan's syndrome, coarctation of the aorta, congenital bicuspid valve and, possibly, pregnancy. Similar degenerative changes in the media of the aorta can be found at autopsy in patients with these disorders even when there is not a dissecting aneurysm present. These same lesions, in milder form, are also seen at autopsy in the general population, increasing in frequency with increasing age. This has led to the conclusion that cystic medionecrosis and the other degenerative changes that are seen with dissecting aneurysm may be nonspecific processes occurring in response to hemodynamic stress, appearing earlier and with greater severity when these forces are increased by hypertension or anatomical abnormalities or when an underlying disorder of connective tissues makes the media less resistant to the normal forces.

The primary event which leads to dissection is

TABLE 1.—*Symptoms in Dissecting Aneurysm of the Aorta*

Cardiorespiratory
Pain (anterior chest, back, epigastrium)
Dyspnea
Hemoptysis
Neurologic
Depressed sensorium
Paralysis (hemiparesis, paraparesis, monoparesis)
Syncope
Transient blindness
Gastrointestinal
Abdominal pain
Nausea and vomiting
Hematemesis, melena
Dysphagia
Renal
Hematuria
Oliguria

a subject of debate. A number of investigators feel that an intimal tear initiates the process, while others feel that there is rupture of the vasa vasorum with bleeding into the weakened media. In support of the latter theory is the observation that in 10 percent of the cases no intimal tear can be found.[1] Regardless of which process is primary, dissection of blood and separation of the media may extend from the point of origin both proximally towards the base of the aorta and distally along its length. Occasionally the process may end distally with a second intimal tear creating a site of re-entry for the dissecting blood. This produces what has been termed a double-barrelled aorta and in some cases has been associated with a prolonged survival even without specific therapy.

De Bakey and his co-workers[3] have devised an anatomical classification of dissecting aneurysm which is based on the site of the intimal tear and the extent of the dissection. A type I dissection has its origin in the ascending aorta and extends beyond the aortic arch for a variable distance down the descending aorta, often to involve the bifurcation. A type II dissection also begins in the ascending aorta, but stops short of the innominate artery. This is the rarest of the types and is usually seen in Marfan's syndrome. A type III dissection begins just distal to the left subclavian artery and extends down the descending aorta. Occasionally it may dissect retrograde to involve the ascending aorta. The relative frequencies of these different types are 60 to 70 percent for type I and 20 to 30 percent for type III, with much smaller percentages for type II and other rare forms (such as dissection limited to the arch of the aorta) which are not included in this classification.

This percentage breakdown emphasizes the fact that most dissections begin at points of increased aortic wall stress, either in the ascending aorta where the intima and media are exposed to the jet of blood ejected from the left ventricle, or just distal to the left subclavian artery at a point where the more proximal aorta, which moves in a pendular fashion with each heart beat, becomes fixed resulting in production of shearing forces.[4] This classification also has important prognostic and therapeutic implications, which I will discuss in more detail a little later on. At this point, it is sufficient to note that type I and type II aneurysms are much more likely to involve the base of the aorta with resultant aortic regurgitation or rupture into the pericardium with rapidly fatal tamponade, and are thus associated with a much poorer prognosis than type III aneurysms.

Clinically, the great majority of dissecting aneurysms occur in patients past the age of 40. In this age group males predominate 3 to 1 over females, but among younger patients females predominate over males. The latter is probably a result of the increased frequency of dissections that occurs during pregnancy.

Pain is by far the most frequent symptom, being present in greater than 90 percent of cases in most series (Table 1). It is usually sudden in onset, continuous in nature and extremely intense, often being described as tearing or ripping. Its distribution can be variable. In the majority of cases it begins in the anterior chest and may radiate through to the back. Less commonly the pain may be primarily localized to the interscapular region, the epigastrium, the lower back or even to an extremity. However, in a series of cases reported by Lindsay and Hurst,[5] these different patterns did not help a great deal in distinguishing the anatomical site of the dissection.

The pain may be accompanied by dyspnea which may result from aortic regurgitation and congestive heart-failure, leakage of blood into the pleural space or compression of the trachea by the dissecting aneurysm. Occasionally hemoptysis can be seen if there has been bleeding into the lung tissue itself. Neurological symptoms are quite common and may include a depressed sensorium or hemiparesis if the dissection has extended to the innominate or common carotid arteries. Paraparesis may result from involvement of the spinal arteries and paralysis of a single limb may follow

occlusion of its arterial supply with resultant ischemia of the peripheral nerve. In addition to abdominal pain, nausea and vomiting may be present. Rarely hematemesis and melena have been reported.[6] These are ominous signs and reflect either rupture of the aneurysm into the esophagus or involvement of the celiac and mesenteric arteries by dissection with resultant intestinal infarction. Dysphagia has occasionally been reported and has been attributed to compression of the esophagus by the enlarged aorta. If the dissection extends down to involve the renal arteries, hematuria may be present. Hematuria was seen in the patient discussed today, but I think it is more likely explained by the long-standing nephrolithiasis. Oliguria may result if dissection involves both renal arteries.

A history of preceding hypertension has been reported in over 90 percent of the cases in most series, and the majority of patients remain hypertensive during the acute episode, often with remarkably high blood pressures. Tachycardia, tachypnea and fever may also be present (Table 2). Unequal or absent pulses may be found in the neck or the extremities and occasionally a double impulse may be felt over a peripheral artery. The latter has been attributed to different rates of propagation of the pressure wave in the true and false channels.[7]

Unilateral jugular venous distension may result from proximal compression by the dissecting aneurysm; bilateral jugular venous distension may reflect congestive heart-failure or rupturing of the aneurysm into the pericardium with tamponade. On examination of the chest, pulsation of the sternoclavicular joint may be present due to the underlying aneurysm and there may be signs of left pleural fluid if there has been leakage of the aneurysm. Cardiomegaly is seen in over 50 percent of cases, even without the presence of blood in the pericardium. This is probably on the basis of long-standing hypertension. S_3 and S_4 gallops along with other findings of congestive heart failure may be present. The murmur of aortic regurgitation is characteristic of this disorder and is the result of retrograde dissection involving the base of the aorta with the loss of support for the valve cusps. However, it is only seen in about 25 percent of the cases. In type III dissections, as in the case presented this morning, one would not expect this to be present.

A pericardial friction rub may be present from the leakage of blood into the pericardium. This may be a result of myocardial infarction if the dissection has involved the coronary arteries, or secondary to uremic pericarditis if bilateral renal artery occlusion has occurred. With extension of the dissection down into the abdominal aorta, there may be abdominal tenderness or rigidity and rarely a palpable pulsating mass.

TABLE 2.—*Physical Findings in Dissecting Aneurysm of the Aorta*

General	"Shock," elevated blood pressure, tachycardia, tachypnea, fever, unequal or absent pulses
Neck	Jugular vein distension
Chest	Sternoclavicular joint pulsation, signs of left pleural fluid
Heart	Cardiomegaly, S_3 and S_4 gallops, murmur of aortic regurgitation, pericardial friction rub
Abdomen	Tenderness, rigidity, pulsating mass (rare)
Neurologic	Depressed sensorium, hemiparesis, paraparesis, monoparesis
Skin	Ecchymoses

Routine laboratory tests, as might be expected, are not very helpful in making the diagnosis. A normochromic normocytic anemia may be present, as well as a leukocytosis.[6] There may be an increase in serum creatinine, as is seen in the patient discussed today. This may be because of prerenal azotemia or acute tubular necrosis if significant hypotension has occurred, or may result from dissection of both renal arteries. As already mentioned, hematuria may be present on urinalysis. The serum amylase may be elevated if there has been involvement of the superior mesenteric artery by the dissection. In subacute cases there may be mild elevation of the serum bilirubin secondary to resorption of the hematoma.

An electrocardiogram shows left ventricular hypertrophy in the majority of cases. This again reflects the high incidence of hypertension. There may be evidence of myocardial ischemia or infarction on the basis of dissection of the coronary arteries, making the differentiation from an isolated myocardial infarction particularly difficult.[6] A pericarditis pattern may also be seen in a smaller percentage of cases.

Chest x-ray films classically show a widened mediastinum (Figure 1). Occasionally a double aortic shadow may be seen, especially if calcification of the intima is present allowing one to see the increased thickness of the aortic wall.[6]

The definitive study, however, is angiography—for which there are currently two accepted techniques. One involves injection of dye into the superior vena cava, or right atrium, with visuali-

zation of the aorta following passage of the dye through the pulmonary circuit. In a series from the Massachusetts General Hospital using this technique, it was found that adequate opacification of the dissecting aneurysm was obtained in all but one of 24 patients.[8] The obvious advantage of this approach is that it avoids the danger of direct trauma to the dissecting aneurysm.

At other centers, and here at the University of California, catheterization of the aorta using the Seldinger technique with direct injection of dye is preferred. The danger of producing rupture of the aorta by the injection is felt to be minimal by those favoring this technique, as long as small injections under low pressure are initially used to determine the position of the catheter. In a series of 27 patients studied in this manner, no complications were reported to have occurred and the procedure was felt to provide far better visualization of the intimal tear and the extent of the dissection than could be obtained with intravenous angiography.[9]

The case for today demonstrates some of the findings seen on angiography (Figures 2 and 3). Usually there is narrowing and displacement of the true lumen medially.[8] Initial opacification of the false lumen may indicate the site of the intimal tear. The dye may then extend and opacify the remainder of the false channel, being separated from the true channel by a thin septum. In instances when the false lumen cannot be opacified, either because there is no intimal tear or because thrombosis has occurred, an increased thickness of the aortic wall lateral to the true lumen usually can be detected.

The prognosis for patients with dissecting aneurysm who do not receive some form of therapy is rather dismal. The survival data from the six largest series in the literature when combined revealed an immediate mortality of 18 percent.[6] After 24 hours only 62 percent of the patients were alive and after a week only 30 percent, after a month 15 percent and after a year only 8 percent were still living. The survival rates for the various form of dissecting aneurysm, however, differ significantly from one another. This fact must be kept in mind when evaluating different forms of therapy. Patients with type I or type II aneurysms have a much poorer prognosis than those with type III due to the increased incidence of aortic regurgitation with resultant heart failure, and of rupture into the pericardium with tamponade.[5]

Despite the long recognition of this disorder and its extremely poor prognosis, specific therapy has only been attempted on a significant scale and with any semblance of success over the past 15 to 20 years. Beginning in the 1930's sporadic attempts were made at creating a re-entry site for the false lumen but no long-term survivals were reported. In 1955 De Bakey and others[10] first reported a series of six patients with dissecting aneurysm treated by surgical resection and graft replacement, four of whom survived for prolonged periods. In 1965 the same group[3] reported 179 cases, again treated with resection and graft replacement in which there was a 21 percent early mortality but a five-year survival of 50 percent, clearly much better than the natural history of this disease. However, other groups at other centers had difficulty matching these surgical results. This difference was partly due to inadvertent exclusion of higher risk patients through the process of referral in the De Bakey series, resulting in a higher percentage of type III patients.[4]

Faced with the significant surgical mortality for acute dissecting aneurysm, Wheat and Palmer[4] in the early 1960's began treating patients with aggressive antihypertensive drug therapy. Their approach was based primarily upon the observation that dissecting aneurysms occurred in the setting of severe hypertension, but also upon experimental and theoretical considerations.

Turkeys previously had been noted to have a high incidence of dissecting aneurysm which could be increased markedly by feeding them beta amino proprionitrile. Using turkeys fed in this manner as a model for human dissection, Simpson, Kling and Palmer[11] found that chronic administration of reserpine or propranolol decreased the occurrence of dissections. This effect, however, was seen even when low doses which produced no significant change in the blood pressure were given. In addition, Prokoff and Palmer[12] using an *in vitro* model of the aorta demonstrated that nonpulsatile flow even at high pressures did not produce dissection, while pulsatile flow at the same or lower pressures did so readily.

To explain these findings, Wheat and Palmer[4] have proposed that the pressure gradient created by the pulse wave is the force responsible for dissection rather than high intraluminal pressure per se. Based upon this explanation, they have recommended the use of antihypertensive drugs which specifically lower this pressure, such as drugs that lower the rate of rise of the pressure

wave (or dp/dt). Their approach, however, must be tempered by the realization that few drugs have had their effect on aortic dp/dt adequately studied. Agents such as propranolol depress myocardial contractility and decrease maximum intraventricular dp/dt, but may or may not have a significant effect on aortic dp/dt at doses commonly used in man. In addition, lowering the peripheral arterial resistance, the heart rate, and the venous return to the heart all decrease maximum intraventricular dp/dt[13] and presumably aortic dp/dt. Thus, some antihypertensive agents may effectively lower aortic dp/dt even though they may not significantly depress myocardial contractility, providing reflex tachycardia and increased cardiac output are prevented.

Based upon the above considerations, theoretically appropriate drug regimens for the treatment of dissecting aortic aneurysm have evolved over the past few years, mainly through the work of Wheat and Palmer. For initial management trimethaphan has generally been used and is probably most ideal. It is given intravenously and has a rapid onset of action. It decreases venous return to the heart, reducing cardiac output, and directly lowers peripheral arterial resistance. Trimethaphan's major drawback is the development of tachyphylaxis, which usually occurs within 48 to 72 hours.

Another agent which has not been used widely, but might be considered for the initial lowering of blood pressure, is nitroprusside. It is administered intravenously and has a rapid onset of action. As a direct vasodilator it lowers both peripheral arterial resistance and venous return to the heart. The main advantage of nitroprusside lies in its almost uniform effectiveness in lowering the blood pressure, as opposed to the tachyphylaxis often seen with trimethaphan.

Intramuscularly administered reserpine has been used in the past, both to acutely lower the blood pressure and for its negative inotropic effect. However, the great variability in both its antihypertensive effect and its onset of action when given by this route, is probably sufficient reason to avoid this form of therapy. Guanethidine and methyldopa have also been used extensively to provide long-term control of the blood pressure after its initial lowering with trimethaphan. Propranolol has been given for its theoretic value in decreasing aortic dp/dt through its depressant effect of myocardial contractility. It also has the advantage of preventing reflex tachycardia in response to lowering of the blood pressure. The obvious hazard of its use, however, is the risk of developing heart failure. Hydralazine though an effective antihypertensive agent, has generally been avoided in the treatment of dissecting aneurysm since theoretically the reflex increase in heart rate and cardiac output that are commonly seen with its use might be harmful.

The largest reported series of cases with dissecting aortic aneurysm treated by drug therapy is that of Wheat et al.[14] They administered trimethaphan initially to acutely lower the blood pressure, followed by guanethidine and reserpine for long-term management. Surgical procedures were used only if there was leakage of the aneurysm, severe aortic regurgitation or occlusion of major arterial branches. Among 50 patients managed with drug therapy alone, the initial mortality was 14 percent. After one year the survival rate was 84 percent, after two years 70 percent and after three years 62 percent—clearly a substantial improvement over the natural history of the disorder and over earlier surgical series. A more recent series of 33 medically treated cases from the Massachusetts General Hospital reported a slightly lower survival rate: 52 percent after a mean follow-up of 43 months using a regimen of trimethaphan, reserpine and methyldopa.[15] However, among six patients with involvement of the ascending aorta there was a much higher mortality with only two surviving long-term.

Similar poor results for the medical treatment of type I and II dissections were observed by Dailey and Shumway[16] at Stanford. In their series only 33 percent of the patients with dissection of the ascending aorta that were treated medically survived, while 72 percent of those treated surgically survived. Among those patients with dissection limited to the descending aorta, the survival rate was similar for medical and surgical treatment, around 80 percent.

The main, immediate complication of medical treatment is severe hypotension which may lead to acute tubular necrosis and renal failure. Late complications are generally the result of delayed progression of the dissection and include retrograde involvement of the aortic root with aortic regurgitation, and the development of saccular aneurysms which are prone to rupture. Either complication requires surgical repair.

Wheat has recently published a practical approach to the management of patients with dissecting aneurysm[17] and I would like to conclude

TABLE 3.—*Management of Dissecting Aneurysm of the Aorta*

1. *Admit to Intensive Care Unit*
   Monitor blood pressure, urine output, left ventricular filling pressure, electrocardiogram
2. *Control blood pressure*
   Trimethaphan intravenous drip to rapidly lower blood pressure
   Oral antihypertensive agent (guanethidine, methyldopa) for maintenance
   Reserpine, propranolol to decrease dp/dt (of theoretical but unproven benefit, congestive heart-failure a hazard)
3. *Aortography* (following control of blood pressure and pain)
4. *Type I and type II*
   Early surgical repair indicated
   Uncomplicated type III
   Continue drug therapy
5. *Surgical procedures indicated for type III complicated by*
   a. Extension into ascending aorta with aortic regurgitation
   b. Occlusion of a major artery
   c. Leakage of blood into the pericardial or pleural spaces
   d. Acute saccular aneurysm
   e. Continued progression of dissection

by summarizing some of the points that he makes (Table 3). If a patient is suspected of having a dissecting aneurysm he should be admitted to an intensive care unit where his blood pressure, urine output, left ventricular filling pressure and electrocardiogram can be closely monitored. If the patient is hypertensive, the blood pressure should be brought down into the normal range. This can be accomplished acutely with trimethaphan or possibly nitroprusside in refractory cases. Along with this initial antihypertensive therapy, or in the minority of patients who present with normal blood pressures, propranolol may be added to help prevent reflux tachycardia and for its theoretical advantage in decreasing dp/dt. Reserpine has been used for this purpose also, but propranolol is probably the better drug.

At the same time the patient should be started on an oral antihypertensive agent, such as guanethidine or methyldopa, for maintenance with anticipation of the development of tachyphylaxis to trimethaphan which usually occurs within 48 to 72 hours. Once the patient is stabilized and there has been control of the blood pressure and relief of pain, aortography should be performed.

If the dissection begins in the ascending aorta, a De Bakey type I or II dissection, early surgical repair is indicated. If no intimal tear is found or if the dissection begins distal to the left subclavian artery, drug therapy should be continued. However, if there is subsequent retrograde involvement of the ascending aorta with aortic regurgitation, occlusion of a major arterial branch, leakage of blood into the pericardial or pleural spaces, or development of a saccular aneurysm, surgical repair should be carried out.

The long-term care of these patients, whether initially treated medically or surgically, should include a carefully controlled antihypertensive drug regimen and possibly a negative inotropic agent such as propranolol. These patients should be followed closely for any return of pain which might signal the recurrence of dissection and for the development of late complications such as aortic regurgitation and saccular aneurysm.

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Important Advances in Clinical Medicine

Epitomes of Progress—Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Plastic Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Plastic Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Orbitocranial Surgery

WITHIN THE PAST FEW YEARS a new subspeciality of plastic surgery has come into being. It is called orbitocranial or craniofacial surgery and it borrows ideas and techniques from both maxillofacial and neurological surgery. Sir Harold Gillies and others pioneered this type of surgery as early as 1949, but it was not until the detailed, systematic work of Paul Tessier in Paris, beginning in 1958, that the scope of orbitocranial surgery was well enough understood to permit widespread clinical application.

Intercraniofacial osteotomies and the ability to move the orbits surgically in any of three spatial directions, now permit the one-stage correction of such previously untreatable conditions as Crouzon's and Apert's syndromes, hypertelorism and certain severe post-traumatic deformities. It now appears that virtually all craniofacial anomalies are amenable to surgical treatment.

As a result of Tessier's work, craniofacial teams are being organized in many American medical centers. Of particular interest is the treatment of young children with craniofacial anomalies with a view to correcting the deformities before potentially crippling psychosocial and functional dental and occular disturbances become serious problems.

The ultimate long-term results of such procedures cannot be evaluated at this time, but due to Tessier's pioneer work, the first significant steps are being taken in the treatment of heretofore impossibly complex craniofacial defects.

JOHN M. GOIN, MD
ROBERT D. RHODES, III, MD

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Subcutaneous Mastectomy with Implant Replacement

INCREASING INTEREST is being focused on the procedure of subcutaneous mastectomy followed by contour restoration of the breast using an alloplastic implant. The procedure is indicated in certain cases of premalignant disease of the breast. Recurrent fibrocystic disease with a familial history of breast cancer places the patient in a high-risk group for subsequent development of breast cancer. Subcutaneous mastectomy and implant re-

placement may well relieve patient anxiety by eliminating practically all of the breast tissue with its malignant potential. Patient selection for this procedure is important because the cosmetic results and incidence of complications following operation vary with the type of breast that requires reconstruction. Application of the techniques of breast reconstruction with prosthetic implants may also be indicated in selected patients following radical mastectomy, particularly where the pectoral muscles have been spared.

JOHN Q. OWSLEY, JR., MD

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The Use of Pressure in Control of Hypertrophic Burn Scars and Contractures

SCAR HYPERTROPHY AND CONTRACTURE are two of the most frustrating sequelae of thermal injury. Hypertrophic scars may occur in any area of the body except those areas in which the skin is splinted by its attachment to underlying structures (for example, scalp, palms of the hands, soles of the feet and tip of the nose). Contractures usually occur across joints.

The development of hypertrophic scars and contractures is so common, especially in children, that they are frequently accepted as natural consequences of thermal injury.

At the Shriners Burn Institute in Galveston, Texas, it has been shown that these sequelae can be significantly altered and controlled by the use of special techniques. The application of continuous and controlled pressure through the use of custom-formed splints and custom-made, anti-burn scar plastic supports has yielded a high degree of both non-surgical control of scar contracture and hypertrophic scar formation.

The healed burn wound in its early stages is characterized clinically by increased warmth, redness and firmness. This scar is composed of young, actively growing, dynamic tissue which responds readily to many stimuli. This tissue will rapidly shorten if not controlled by an opposing force. The opposing force may consist of splinting, traction, pressure, exercise or a combination of these.

Splints can be easily made by using "orthoplast" isoprene which is simple to cut, mold and adapt. Used properly these splints will decrease contracture formation.

Constant pressure following healing can be applied by the use of elastic wraps or Jobst® gradient pressure garments which are custom made specifically for the burn patient. For maximum effectiveness the garments must be properly fitted and applied as soon as healing and graft take permits. The application of pressure should be constant except for brief periods which should not extend for more than one hour.

These garments must be worn continuously for at least six months and in some cases, longer. The general consensus is that pressure should be applied as long as the scar has the clinical appearance of an active scar, that is, as long as it remains hyperemic and firm.

ANGELO CAPOZZI, MD

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Perils of Body Contouring

THE CONCEPT of "body contouring" has become increasingly popular as shown by reports in professional journals and particularly by a multitude of articles in popular newsstand magazines. Public acceptance of body contouring is evident from the increased requests for such procedures being received in many plastic surgery offices.

Persons who have conscientiously pursued a rigid weight reduction program, often with a loss of more than 100 pounds, are frequently dismayed with the hanging folds of skin and subcutaneous tissue in the face, neck, arms, breasts, abdomen, buttocks and thighs. Despite rigorous exercise programs, the redundant skin cannot be "firmed up" and these patients are ideal candidates for total body contouring. Women who have multiple abdominal striae following pregnancy and persons with congenitally-determined excessive fatty deposits in the buttocks and thighs are also good candidates for body contouring.

Although obvious physical and psychological improvement may be attained by such surgical procedures, the prospective patient must be fully informed of the multiple risks and complications inherent in such procedures. Conspicuous scarring is frequently present postoperatively. Often these

scars can be hidden in areas normally covered with clothing (for instance, the low transverse abdominal scar resulting from abdominal lipectomy). Scars in the thigh lift may be hidden in the groin and buttock folds. The scars resulting from vertical incisions in the thighs or upper arms are impossible to hide when wearing light summer clothing. Most suture lines are closed under moderate tension and this frequently results in wide, hypertrophic or keloid scars. Hematoma, seroma, skin and subcutaneous necrosis, anesthesia and lymphedema may delay recovery for months and produce more patient dissatisfaction than did the presenting complaint.

FRANKLIN ASHLEY, MD
DENNIS P. THOMPSON, MD

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Travase®: An Effective Proteolytic Enzyme in the Treatment of Burns

TRAVASE* is a remarkably effective proteolytic enzyme and is especially useful in the rapid debridement of the acute burn wound. It is known to be 5 to 16 times more effective than any other known debriding agent.

Travase is a broad spectrum natural protease derived from cultures of Bacillus subtilis. It functions by degrading and liquifying complex denatured proteins of the necrotic wound to amino acids and acid soluble peptides.

A clinical evaluation of Travase ointment was begun early in 1971. Sixty-eight patients, ranging in age from one and a half years to eighty-six years, were treated over the ensuing sixteen months. Whenever possible, symmetrical areas were treated with the enzyme and adjacent areas treated without enzymes to serve as controls. Therapy was started as early as the first day in minor second and third degree burns but usually on the second to the fifth day in major burns.

First, the patient is tubbed daily in a Hubbard® tank and loose debris is trimmed. After removal from the tank, a thin layer of Travase is applied to a selected wet area (not more than 15 percent of the burned areas). Then this is covered with the topical therapy of choice, such as silver sulfadiazine or sulfamylon, on fine mesh gauze. A wet occlusive dressing of normal saline is applied above this and may be wrapped by Kerlix® and bias stockinette. This is then moistened every four hours and changed twice daily. The treatment is continued for three to ten days, depending upon the response. A continuous wet dressing is absolutely necessary for optimum and rapid debridement.

In our series of 68 patients, 85 percent were three-quarters debrided within eight days and ready for autografting two days later. Six of our ten failures occurred when treatment was started after the first burn week or when the eschar became leathery and dry. No toxic, allergic or adverse reactions were encountered. There was no interference with normal epithelialization and, in fact, Travase was often helpful in delineating second degree burns from third degree burns. The only side effects noted were occasional mild transient burning pain and occasional bleeding controlled by the occlusive dressing.

In conclusion, Travase, or sutilains ointment as it is known, appears to be a major improvement over the other debriding agents in the treatment of acute burn wound. The burn eschar can be rapidly and safely dissolved if the ointment is properly used and the burn wound can be prepared for skin grafting two weeks earlier than previously possible.

VINCENT R. PENNISI, MD

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Lymphedema of the Extremity

SEVEN PATIENTS WITH LYMPHEDEMA, of either congenital or acquired cause, have been successfully managed by staged subcutaneous excision.

Bed rest with periodic elevation of the extremity was continued for two to five weeks until all edema had resolved. During this period, two units of blood were drawn to be readministered as an autotransfusion during the operative procedure to avoid the dangers of homologous transfusion. The first operative procedure was done on the medial aspect of the lower leg. Flaps were developed anteriorly and posteriorly from a midlateral incision, and all of the underlying subcutaneous tissue and muscle fascia were resected to expose the underlying gastrocnemius muscle. Considerable excess skin was excised upon closure of the wound. The second stage was done two months later on the lateral aspect of the lower leg. When an addi-

*Travase® is a product of Flint Laboratories.

tional procedure was required, it was done on the medial thigh.

To ascertain the effect of the procedure on lymphatic drainage, radioiodinated human serum albumin (RIHSA) clearance studies were made preoperatively and one month and one year postoperatively. In all seven patients RIHSA clearance values were significantly improved one year postoperatively.

These patients have been followed from three to four years postoperatively. Clinically, there was excellent control of symptoms in all patients, as well as reduction in size and return of normal function in the involved limbs.

TIMOTHY A. MILLER, MD

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Hair Transplant Surgery

HAIR TRANSPLANTATION is a technique in which small plugs of hair-bearing tissue are transplanted into non hair-bearing areas, resulting in hair growth. While this is also applicable to coverage in scar alopecia, its most common use is for male pattern baldness. The success of the procedure depends on the fact that hair follicles moved from their original location on the body to another area will behave as they did in their natural site. In male pattern baldness, for example, a horseshoe-shaped fringe of hair usually persists, and hair follicles moved from here to a bald area on the same patient's scalp will take root and grow.

In the procedure, the donor area is clipped and both the donor and recipient areas are anesthetized with a local anesthetic. A circular punch 4 to 5 mm in diameter is used to cut plugs of scalp in both areas. The hair-bearing plugs are placed in the punched-out sites on the bald scalp, while the donor area may or may not be sutured. The clipped area can usually be covered over completely by surrounding hair, so that the donor site does not show, even immediately after the procedure. The head is then bandaged appropriately.

A crust forms over each graft shortly after the procedure and remains attached for 10 to 20 days, after which it separates, leaving a pinkish spot. The clipped hairs in the transplants usually do not grow, but are shed between the second and fourth week after the procedure. A new generation of hair is seen at the surface usually during the twelfth week after transplantation, although up to twenty weeks may be required. These hairs grow at the same rate as they did in their original location. The skin surface of the grafts usually blends in well with the surrounding scalp after a period of 3 to 4 months, although in some patients the grafts may be a shade lighter or slightly elevated. The number of transplant plugs which should be placed at each session and the frequency of transplant sessions depend on the characteristics of each individual case, although usually from 150 to 500 plugs may be required in stages of from 50 to 75 plugs each.

ROGER P. FRIEDENTHAL, MD

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Microvascular Replantation and Transplantation Surgery

EXPERIMENTAL WORK using animals during the late 1950's and early 1960's is beginning to bear clinical fruit in the field of replantation and microvascular transplantation surgery. Malt's first successful human extremity replantation in 1962 has been followed by numerous reports, particularly from China. Dr. Cheng Chung-Wei from the 6th Peoples Hospital in Shanghai speaks from an experience of over 250 digital replantations and over 100 extremity replantations.

The Chinese stress the importance of wide debridement of soft tissue and bone shortening in order to achieve primary nerve and vessel repair. With refrigeration of the part they have been able to replant extremities up to 33 hours after amputation. Postoperative heparin is used with digital replantations, but no anti-coagulants are used with higher amputations because of considerable blood loss. Although recovery may be prolonged after such procedures, the final result is considered worthwhile if the replanted part functions better than a prosthetic device.

It seems logical that replantation centers should be organized regionally in this country to handle these uncommon but often devastating injuries.

The elective transplantation of large flaps by microvascular anastomosis has reached a high level of perfection in Japan. Dr. Harri of Tokyo has used over 80 such transplants instead of the classic tube pedicles or flaps to reconstruct ex-

tensive defects. The hospital stay is reduced by this technique and the patient is spared weeks of uncomfortable immobilization.

Thumb and finger reconstruction by toe transplantation, once a medical curiosity, is being done with increasing frequency. The expanding interest in the field of microsurgery will bring about simplification of techniques and more dependable results.

HARRY J. BUNCKE, MD

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The Eye in Facial Palsy

TODAY, treatment of facial palsy only rarely requires that a deforming central tarsorrhaphy—formerly a common procedure to protect the cornea from dust and dry air—be done. The early intervention of a reconstructive plastic surgeon, with occasional assistance from a soft contact lens fitted by an ophthalmologist, provides ocular protection without creating highly visible deformity.

The condition treated is the abence of the closing force of the orbicularis worsened by the lively action of the levator (lifter) of the upper lid, which now has no antagonist.

The diverse therapeutic choices include operations to support and horizontally shorten the lower lid (some taken from antiquity resemble old operations for the correction of senile ectropion in the central, medial or lateral lid). Other approaches support the lid by use of autogenous or preserved fascia lata graft supports in the pretarsal lower lid, with the delicate assistance of a Scottish lateral tarsorrhaphy to join the upper and lower tarsal plates so the lower lid will rise with the upper and therefore look alive. Such fascial slings often accompany procedures to support the rest of the face.

To antagonize the levator and allow the lid to fall when it relaxes, as in downward gaze or blinking, a weight of gold can be placed in the upper lid to use the force of gravity. More active, and risky, is the use of a stainless steel spring in the upper lid for the same purpose or a fine silicone rubber band around both lid edges which holds the lids closed when the levator is not working. A more active and useful upper lid can be achieved in these ways.

Temporal muscle transfers to replace the orbicularis occasionally work well but frequently fail to achieve a good functional and cosmetic result. Free muscle grafts reportedly work to some extent but are experimental still—as is the use of magnets. The deformity is such that patients are often more than willing to become parties to experimentation.

The options are many; none is entirely satisfactory. The decision as to method of treatment should be made by those with special training, interests and skills in the subject.

RICHARD JOBE, MD

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ADVISORY PANEL TO THE SECTION ON PLASTIC SURGERY

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EDITORIAL

On Training Health Manpower for Primary Care

THE TRAINING OF HEALTH MANPOWER to render primary care is a major goal of both medical educators and government at this time. Substantial sums of money and substantial human effort are being spent to accomplish this. But somehow it has all yet to be got together. Even the goal itself, primary care, has so far eluded precise definition. This makes it uncertain that the right manpower is always being trained for the right task. Therefore, this editorial will examine what is meant by primary care and then suggest that comprehensive primary-care education centers be developed to train manpower for primary care as defined.

At present the concept of primary care appears to take several different forms. To some it means family practice. To others it includes the practice of the general internist and the pediatrician, and sometimes obstetrics and gynecology as well. Still others conceive of it as emergency or triage care, prevention, health maintenance and the continuing care of chronic illness or disability. Primary care is also to be distinguished from secondary or tertiary care and from research, yet obviously these can never be separated completely.

Primary care is also viewed differently by the various parties directly involved. The physician says that primary care is his responsibility and that a primary-care physician should attend all the medical needs of his patients and, where appropriate, the patient's family as well—and that there should be appropriate referrals for specialist (secondary) and subspecialty (tertiary) care where necessary. But there are other health professionals who know that primary physicians, even with the help of specialists, simply cannot reach all of the unreached or do all that needs to be done. These professionals see themselves as "physician extenders" or as practitioners in their own right, able to perform many primary care services with or without direction from physicians. And indeed there are many educational, screening and even patient-care functions which they can and do perform.

The consumer of health care is another party directly concerned and indeed is the raison d'être of primary care. While the consumer may or may not be clear on the niceties of just what is primary, secondary or tertiary care, he now believes he has the right to health care, that the necessary information about what it is should be given to him and that he also should have ready access to it. This makes health education and access just as much a part of primary care as patient care itself.

From this base one may attempt to discuss a conception and even attempt some kind of a definition of primary care. Primary care seems to be that which is found at the operational interface of the public with the health care system. There are a number of facets to this operational interface. Both patients and the public generally must be educated about their own health and health care and taught to know when they should seek help. This is part of primary care. When they need help or think they do, there should be easy and effective access to the health care system. This too is really part of primary care. Then primary physicians and allied health professionals working together should be able to provide emergency care, episodic care, continuing care, health maintenance and prevention services. And to complete this primary care, there should also be easy access to, and interaction with, readily available secondary and tertiary care resources.

If a more or less definitive conception such as has been stated can be accepted, then it becomes possible to begin identifying more precisely what is involved in the training of health manpower for primary care. There is no question but that it involves the training of primary care physicians. There is also no question but that it involves the training of allied professionals and that both physician and the allied health professionals should gain some training experience in working together

where the needs and problems are, and this probably means where there is a need. And another sine qua non is a close relationship with a major health science center which can bring its specialty, subspecialty, educational and even research resources to bear upon the education and training of health manpower for primary care. This is essential to assure the quality of the educational programs and that they will remain in contact with, and responsive to, progress in the mainstream of scientific medicine.

If all this is true, then perhaps it is time to place the education and training of health manpower for primary care into a somewhat broader framework, some such framework as has been suggested. Perhaps there is a viable role for a primary-care education center which will be sensitive and responsive to health manpower needs for primary care and at the same time will be closely linked to a major health-science education and research center. Bits and pieces of such a center are already to be found here and there, but a truly comprehensive primary-care education center, focused on developing the professional skills which are needed, located where the action is and linked to a major health science center, has yet to come into being.

There are opportunities to do this in many parts of the West, and the need for such a model exists.

—MSMW

Sicknesses of the Sinus Node

THE SUBJECT of the sinus node being close to my own heart, I was more than usually interested to read the fine specialty conference by Scheinman and his colleagues in this issue of the JOURNAL. It is an excellent compilation of basic information coupled with logical clinical application. As such, it deserves the careful perusal it will undoubtedly attract among those caring for patients with abnormalities in electrical stability of the heart. Hirschfeld in this conference properly defines and emphasizes the frequency of syncope in patients primarily having disorders involving the sinus node, but also adds that such disease is seldom isolated, for accompanying abnormalities elsewhere in the heart are the rule rather than the exception. Two general ways of testing the function of the sinus node are clearly reviewed by Abbott and Kunkel, after first pointing out that repeated or prolonged monitoring (for example, with a Holter device) may provide all the specific data one requires for clinical management. Monitoring alone, however, is not always successful for the purpose. This is illustrated by the one patient in whom abnormal function of the sinus node was noted on a single electrocardiographic tracing though the abnormality was never shown during monitoring study. Abbott explains the rationale and methods for doing a variety of tests short of electronic pacing, while Kunkel presents the special array of electronic pacing techniques now available to test the condition of the sinus node.

In Abbott's review two things are of particular clinical importance. One is the documentation of abnormal function by the sinus node during exercise stress testing; this is not so surprising to me as is the usual usefulness of sinus rate as a criterion of cardiac performance during exercise. Actually, I would expect an even higher rate of abnormal function by the sinus node and therefore even less predictability of sinus rate in patients with most forms of heart disease. The second thing is the clear demonstration of important symptoms such as pre-syncopal dizziness, directly related to abnormalities of cardiac rhythm in some of his patients who were stressed.

Kunkel made his case remarkably well by showing a prolonged sinus node recovery time in 16 of 21 patients he studied with electronic pacing. This proves the sluggishness of the abnormal sinus node in resuming dominance once it has been suppressed by overdriving. It might have been worth while to make it clearer that overdriving requires relatively normal atrionodal conduction (that is, into the sinus node), just as normal sinus rhythm requires good sino-atrial conduction. If the over-driving stimulus has difficulty penetrating the sinus node, then the node may resume its own automatic function faster than if it is successfully engaged by the overdriving stimulus.

In the last section Scheinman synthesizes the preceding findings into their optimal value for clinical applicability. He correctly emphasizes that results of vagolytic or sympathomimetic drug therapy have been disappointing in the majority of patients with abnormal function of the sinus node.

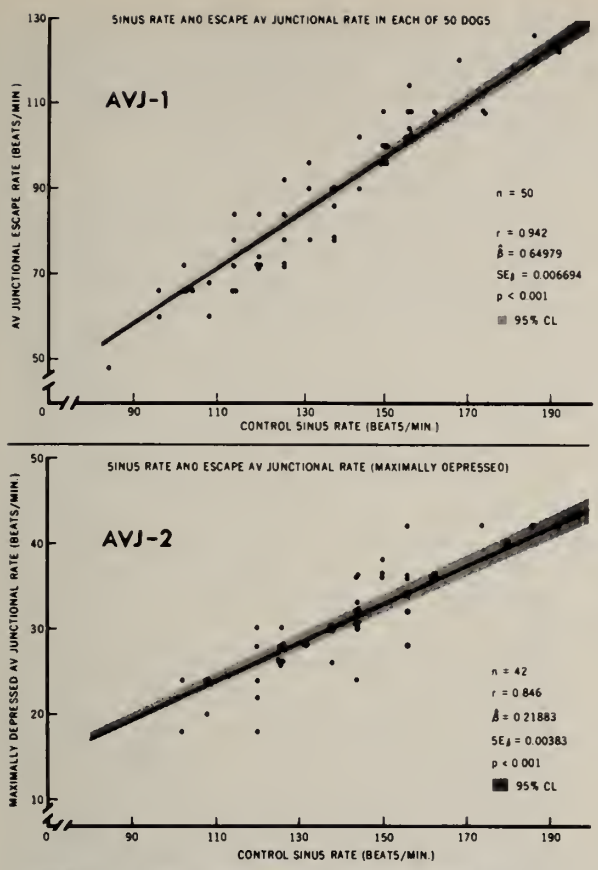

Figure 1.—These two graphs depict two different types of AV junctional rhythm experimentally produced in the dog. AVJ-1 emerges consistently when the sinus node is selectively suppressed.[1] AVJ-2 is the only escape rhythm observed after selective pharmacologic production of complete AV block.[2]

He also explains the variability in frequency of clinical symptoms, with long asymptomatic periods in some patients, and the influence this has on both clinical and monitoring evaluations by the physician.

Just as disease of the sinus node seldom occurs without accompanying histological abnormalities elsewhere in the heart, it is equally important to appreciate the physiological relationship between sinus rhythm and the usual forms of escape rhythm. In two recent studies in anesthetized dogs my colleagues and I found that there is a consistent mathematical relationship between sinus rate and two forms of atrioventricular (AV) junctional escape rhythms. When the sinus node was selectively suppressed by direct perfusion through its nutrient artery with substances having a negative chronotropic effect, a single type of AV junctional escape rhythm emerged at a rate which was 66 percent of the sinus rate.[1] If the AV junction was

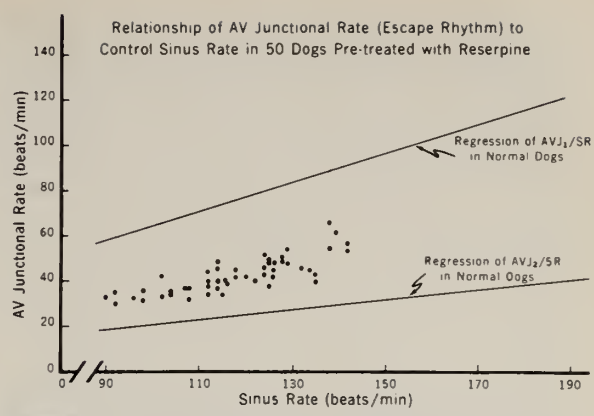

Figure 2.—After removal of adrenergic neural tone (here by pre-treatment with reserpine), AVJ-1 emerges erratically and eventually stabilizes at rates (black dots) much slower than normal.[2]

selectively perfused with neostigmine via the AV node artery, there appeared an expected complete AV block followed by the emergence of a second single form of AV junctional escape rhythm, but this one was only 22 percent of control sinus rate.[2] These mathematical relationships were highly significant ($p<0.001$). The ratios of sinus rate to the first AV junctional escape rhythm (AVJ-1) to the second form of AV junctional escape rhythm (AVJ-2) may be expressed as SN: AVJ-1 : AVJ-2 = 9 : 6 : 2 (Figure 1). Perhaps of equal importance was the fact that no other form of escape rhythm ever emerged in any of the experiments, raising the question of whether there is any stable form of automaticity beyond the region of the AV junction in an intact heart.

Furthermore, we have recently found that both of the normal automatic centers of the canine heart are dependent on adrenergic neural tone for their normal performance as judged from rate, but that the AV junction is much more dependent than the sinus node.[3] Circulating catecholamines played little role in this dependence or its evasion. When adrenergic neural tone was selectively eliminated by a variety of procedures, then AV junctional rhythm would only emerge slowly and erratically after the selective suppression of the sinus node. How the eventual rate of AV junctional escape rhythm in dogs pre-treated with reserpine relates to the rates of normal AVJ-1 and normal AVJ-2 is illustrated in Figure 2. Since a number of currently popular anti-arrhythmic drugs have important effects on adrenergic neural responses, these observations may have special relevance in the presence of a sick sinus node.

Finally, a word about words. There is something

about "sick sinus" which gives me a queasy feeling. While I know that sinus arrest and sinus rhythm are terms in such common usage that they have every legitimacy, we do still say abnormal sinus node instead of abnormal sinus, and the phrases sinus node dysfunction and sinus node disease are sprinkled throughout the present estimable review by Scheinman and his colleagues. Instead of succumbing to the sibilant alliteration of sick sinus syndrome, I suppose I would be happier if we stuck with sick sinus node or something like that. All that aside, the review on the subject is excellent and anyone dealing with patients having abnormal cardiac rhythms will profit from carefully reading it.

THOMAS N. JAMES, MD
Professor and Chairman
Department of Medicine
The University of Alabama
School of Medicine
University Station, Birmingham

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The Clergy and Patient Care

THERE HAS BEEN RELATIVELY little discussion in the medical literature about the role of the clergy in patient care. Yet the clergy is playing an important part in patient care and probably should play an even greater one. These are times when many religious denominations are reaching out and addressing community and social problems. As a part of this trend more and more clergy are to be found working in hospitals. Medicine and patient care are also undergoing significant change as a result of scientific progress and the new consumerism which in many ways is profoundly affecting medical practice—and will continue to do so.

Both the clergyman and the physician minister to human beings and both have a common interest in the betterment of mankind. Both are concerned with the health or wholeness of each person, and yet both are also concerned with the well-being of mankind in the aggregate. Both have a particular interest in the sick and with the problems of those who cannot cope. And each has a rich experience and a scholarly discipline to bring to bear.

It is suggested that there may be three roles for the clergy in patient care, one traditional, one fairly new and the other quite new. Traditionally the clergyman visits the sick, comforts the family and, depending on the beliefs and attitudes of the patient, is able more or less effectively to assist a patient or a family who is not able to cope for whatever reason. For the deeply religious who have a strong tie to their church and to their clergyman, this can be a powerful force in patient care. It is gratefully recognized by the responsible physician when it can be brought to bear to give a very ill patient comfort, courage and will to live or endure, or to calm a distressed or distraught family.

The second suggested role for the clergy in patient care is somewhat new. It is really an extension of the counseling function of the clergy. It derives from the new consumerism in medical care and the recent legal doctrine of "informed consent." This doctrine weakens the role of the physician in patient care by placing the responsibility for what shall and shall not be done in his care more directly upon the patient. If the patient desires, the physician is obliged to explain fully the pros and cons of each possible course of action to the patient who then decides what shall or shall not be done. This puts an enormous, and sometimes unfair, burden upon a patient or a family who may simply just not be able to cope. It is suggested that here may be a role for the clergy. It is a counseling role, that of a sympathetic, wise and experienced person who as friend, minister or priest can help the weakened or distraught patient and his family find their way to the decision which must be made. This role for the clergy is presently being developed in many hospitals.

A third suggested role, one which is only beginning to be perceived, pertains to issues of decision making in medicine which may extend beyond what may be best for a particular patient in a given circumstance. Medical science is bringing many larger problems of morality, ethics and justice into focus in patient care. Many of these issues are truly mind boggling. They relate to the quantity and quality of the population and to the limited resources which society and the planet can bring to bear to accomplish what is becoming

scientifically possible and on the scale which is needed. Issues of morality, ethics and justice are surfacing rapidly. These are issues which seem to call for the rich experience and scholarly discipline of the clergy, as well as the physician's broad knowledge of the problem, what is likely to happen and what can be done about it.

Thus it appears that there is much the clergy can contribute to patient care. There is surely a common ministry awaiting both physicians and clergy for the betterment of mankind. There is a need to get on with it.

—MSMW

Pseudomembranous Colitis

RECENTLY THERE HAS BEEN a resurgence of interest in a previously well-recognized clinical problem, pseudomembranous colitis. This disorder has been reported recently in association with the administration of various antibiotics such as ampicillin,[1,2] lincomycin[3] and clindamycin.[4-6] The paper by Keeffe et al in this issue of the JOURNAL is a report of six cases and a review of the recent literature which summarizes adequately our current state of knowledge.

Several issues are raised by this article. In two of the cases (numbers 1 and 5), a definite association between pseudomembranous colitis and antibiotics can be questioned because both were in a setting where vascular insufficiency or surgical intervention or both may have played an etiologic role. Moreover, in some of the 42 cases reviewed from the literature by Keeffe et al, it is not clear whether antibiotics played only a contributory role or no role at all. Thus, any conclusions drawn from cases where the causes may be multiple may be misleading. In Case 1, small bowel involvement with pseudomembranes is mentioned. Most observers have not reported this finding in drug-induced colitis, but it has not been well studied and deserves further investigation.

How common, then, is drug-induced pseudomembranous colitis, and can it account for the frequency with which cases have recently been reported? The Upjohn Company has published a letter to physicians stating that the incidence of "serious colitis" following administration of clindamycin is in the range of one in 50,000 to one in 100,000. This information is in striking contrast with a prospective study[7] of 200 patients in hospitals who were given clindamycin for various reasons. In that study, diarrhea (21 percent) and pseudomembranous colitis (10 percent) were frequently found. Since all symptoms disappeared on withdrawal of the drug, these cases were presumably drug related. Some of the reasons for the very low incidence of colitis reported by the Upjohn Company are explained in the manner in which their data were obtained. The numerator is low because there were many cases not diagnosed or reported. Moreover, the term "serious colitis" would tend to eliminate those cases discovered early and treated appropriately before serious sequalae occur. The denominator in their data is high because it refers to total doses prescribed, not necessarily taken. Thus, the two incidence figures are not comparable.

In the prospective study[7] pseudomembranous colitis developed more frequently after oral administration of clindamycin, but was also seen with parenteral administration of the drug. The age of patients with colitis ranged from 15 to 87 years and 70 percent of them received clindamycin as the only antibiotic. The majority of patients who developed colitis were treated for minor illnesses and did not have any serious underlying pathologic process. This differs from findings in the scattered cases reviewed by Keeffe et al, in which many of the patients had serious diseases, some of which might predispose to—or be the sole cause of—pseudomembranous colitis. Most cases of colitis present with profuse, watery, nonbloody diarrhea. Fever and abdominal pain by themselves are not diagnostic for pseudomembranous colitis. The diagnosis can *only* be made by careful sigmoidoscopic examination since half of the patients with diarrhea do not have pseudomembranes. In advanced cases, the radiographic findings in a significant percentage of patients with pseudomembranous colitis may be very specific and closely reflect the actual findings at sigmoidoscopy and colonoscopy.[8]

Pathological examination may confirm the diagnostic impression obtained by sigmoidoscopy, but is no more accurate. However, in order to made a precise diagnosis, rectal biopsy should be done in all cases of suspected pseudomembranous colitis. Analysis of 23 rectal biopsy specimens in clindamycin-associated colitis has shown the diffi-

culties that can arise both in sampling and in handling the tissue.[9] Although a characteristic feature of pseudomembranous colitis observed in autopsy material is the presence of notably dilated, actively secreting glands subjacent to the pseudomembrane, this change was observed in only eight of 23 patients.[9] It was almost as common (six of 23) to see biopsy specimens in which the goblet cell population was depleted. While necrosis of surface epithelium was a frequent finding, especially beneath the pseudomembrane, true ulceration was not a feature of pseudomembranous colitis. Aside from the pseudomembrane itself, the most characteristic pathological feature of the colitis was an intense polymorphonuclear infiltrate, which was either totally confined to the mucosa or was associated with minimal submucosal inflammation. Crypt abscesses were not seen.

Although prospective analysis of appropriate therapy for pseudomembranous colitis has not been done, supportive therapy (such as bowel rest and vigorous fluid and electrolyte replacement) seems appropriate. Steroids have not been shown to alter the natural history of drug-induced pseudomembranous colitis. Ileostomy or subtotal colectomy is sometimes necessary to control diarrhea and protein loss in severe cases.

While the mechanism by which antibiotic therapy leads to colitis is unknown, the awareness of antibiotic-associated diarrhea and colitis should lead to early diagnosis by sigmoidoscopy, cessation of antibiotic therapy and supportive therapeutic intervention. This approach should greatly decrease the morbidity and almost eliminate the mortality of pseudomembranous colitis. Any physician who is aware of the possibility of colitis and its clinical presentation should not be reluctant to use clindamycin or other antibiotics when indicated.

Francis J. Tedesco, MD
David H. Alpers, MD
Gastroenterology Division
Washington University School of Medicine
St. Louis

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CASE REPORTS

Refer to: Levine VD, Overturf GD, Mathies AW: Shigella dysenteriae type 1—Severe dysentery and sepsis with hematologic, hepatic and renal complications. West J Med 121:501-504, Dec 1974

Shigella Dysenteriae Type 1

Severe Dysentery and Sepsis with Hematologic, Hepatic and Renal Complications

VICTOR D. LEVINE, MD
GARY D. OVERTURF, MD
ALLEN W. MATHIES, PhD, MD
Los Angeles

BACILLARY DYSENTERY caused by Shigella dysenteriae* (Shiga dysentery) has occurred rarely in the United States, accounting for fewer than 1 percent of Shigella isolates up to 1969.[1] In early 1969, an epidemic strain of Shigella dysenteriae type 1 was responsible for a widespread epidemic in Guatemala and elsewhere in Central America.[2,3] In recent years, increasing numbers of cases (including two deaths) have been noted in Los Angeles.[4] Most domestic cases have been secondary to foreign importation, although some of the patients acquired the infection in the United States.

Since it was first recognized, in the latter part of the nineteenth century, Shiga dysentery has been associated with both clinical severity and high mortality.[5] The clinical dissimilarities from disease caused by other Shigella serotypes and its rare appearance in the United States emphasize the need for review of the illness caused by this organism. This report concerns several of the complications encountered in a severe case of Shiga dysentery.

*S. dysenteriae is the type species of the genus Shigella; subgroup A of shigellae which characteristically do not utilize manitol and are serologically distinct (serotypes 1-10) from members of the other subgroups (B,C,D).

From the Department of Pediatrics and Medicine, University of Southern California and the Communicable Disease Service, Los Angeles County/University of Southern California Medical Center, Los Angeles.

Submitted, revised, April 1, 1974.

Reprint requests to: G. D. Overturf, MD, LAC/USC Medical Center, General Laboratories Building 2-G-24, 1129 North State Street, Los Angeles, CA 90033.

Report of a Case

A 16-year-old Mexican boy was admitted to the Communicable Disease Service of Los Angeles County-University of Southern California Medical Center (LAC/USC) on August 22, 1973, with complaint of diarrhea for four days. The patient had resided on a farm in Zamora, Mexico, and had come to visit the United States on August 17, 1973.

Four days before admission to hospital he noted onset of mild fever, crampy abdominal pain, and diarrhea consisting of 10 to 12 green, bloody, watery stools a day. The following day the patient no longer noted fever, but had nausea and profound vomiting. The day before admission (August 21), the patient was evaluated in the Communicable Disease admitting room and was found to have blood pressure of 118/75 mm of mercury, pulse rate of 76 and temperature of 37°C. The body weight was 53.0 kg. Other than increased bowel sounds and mild abdominal tenderness on palpation, the findings on physical examination were within normal limits. Laboratory data included hemoglobin of 18.8 grams per 100 ml, hematocrit 57 percent, leukocytes 8,000 per cu mm with 10 percent segmented and 48 percent banded forms, 26 percent lymphocytes, 13 percent monocytes, 1 percent basophils, 2 percent metamyelocytes and an occasional myelocyte. Platelets were normal in number. Blood sugar was 155 mg per 100 ml, blood urea nitrogen 14 mg per 100 ml, sodium 135 mEq, potassium 3.6 mEq, bicarbonate 31 mEq and chlorides 89 mEq per liter. On microscopic examination, the stool was watery and bloody with sheets of polymorphonuclear leukocytes. No ova or parasites were present. The evaluating physician's assessment noted the normal hydration and the absence of toxicity. The patient was sent home with instructions to take a clear liquid diet. The following day he returned with persistence of vomiting, an increase in bloody diarrhea, and dehydration.

On admission (August 22) the patient appeared only mildly toxic. The blood pressure was 110/70 mm of mercury, the pulse rate 100, respirations 36 per minute and temperature 37.2°C. The neck was supple, the chest clear, and findings on exami-

nation of the heart normal. The abdomen was not distended. Hyperactive bowel sounds were noted and there was mild diffuse tenderness and voluntary guarding. The liver and spleen were not enlarged. Examination of the skin showed no abnormalities except for decreased skin turgor. Body weight was 4.5 kg less than it had been the preceding day. There was no lymphadenopathy and no abnormality was noted on neurologic examination. Admission laboratory studies showed serum sodium of 126 mEq per liter and a BUN of 20 mg per 100 ml. Leukocytes numbered 12,400 per cu mm and there was still a pronounced shift to the left in cell differential. Platelets were present in adequate numbers. The hemoglobin content was 20.2 grams per 100 ml of blood and the hematocrit was 61 percent.

The impression on admission was of acute Shigella dysentery with decided fluid volume depletion, and therapy was begun accordingly. The patient was offered nothing by mouth and large amounts of fluids were given intravenously—14.0 liters over the first 72 hours. The patient continued, however, to have an output of 20 to 30 bloody stools a day totaling 4 to 6 liters, with little concurrent urine output. He remained afebrile, complaining of only mild to moderate crampy abdominal pain. During this time the blood pressure ranged from 110/70 to 90/60. Stool cultures obtained on August 21 grew Shigella dysenteriae type 1. A seven-day course of ampicillin, 150 mg per kg of body weight per day, intravenously, was begun on the second hospital day. Blood cultures obtained before therapy on August 23 also grew S. dysenteriae type 1. Susceptibility studies showed resistance to chloramphenicol, tetracycline, sulfonamide, and streptomycin, and susceptibility to ampicillin.

On the second hospital day, the patient's urinary output fell to less than 200 ml in 24 hours with a concurrent rise in the specific gravity to 1.030. Serum sodium fell to 116 mEq per liter. During the course of rehydration and with continued gastrointestinal hemorrhage the patient's hematocrit fell to 30 percent. The platelet count fell to 8,000 per cu mm by the third hospital day and fragmented red blood cells were seen on peripheral smear.

The Quick prothrombin time, partial thromboplastin time and thrombin time were all mildly prolonged. The result of a protamine test was positive, while fibrinogen showed a titer of 1:256 (>400 mg per 100 ml) and a factor VIII level was 223 percent. In addition, the patient was noted to be jaundiced, and liver function tests showed albumin of 1.9 grams, globulin 1.9 grams, and total bilirubin 7.0 mg per 100 ml (with 2.8 mg direct). Alkaline phosphatase was 3.3 B.L. units, SGOT 139 units, SGPT 37 units, and LDH 5,965 units. Abdominal distension developed concurrently with a gradual loss of bowel sounds and abdominal x-ray films were consistent with a paralytic ileus. By the third hospital day, ascites and peripheral edema became evident on physical examination.

Over the following week the serum creatinine rose from 1.2 to 7.1 mg and the BUN from 33 to 140 mg per 100 ml. Urinalysis during this time showed only minimal proteinuria and microscopic hematuria, without red cell casts. Urine output increased gradually during this time but progressive azotemia did not improve. On the fifth hospital day the leukocyte count reached 90,000 per cu mm, with numerous immature precursors seen on peripheral smear. On examination of bone marrow aspirate, there was evidence of pronounced toxic effect on all cell lines, including megakaryocytes which appeared slightly decreased in number. During this time the patient required 12 blood transfusions and 10 platelet packs due to gastrointestinal hemorrhage.

On the seventh hospital day (August 29) a Scribner shunt was placed in the patient's right arm and hemodialysis was carried out four times over the next eight days. Hepatic and renal dysfunction gradually resolved, with general improvement in his condition during dialysis. The bloody diarrhea which had persisted throughout the first two weeks in hospital gradually resolved during the third hospital week.

At the time of discharge on September 18, 1973, the patient was asymptomatic, with normal appetite, normal bowel movements, and no edema. Creatinine content was 1.5 mg per 100 ml, liver function tests were normal, and urinalysis was normal. The thrombocytopenia had resolved; however, the patient remained anemic; hemoglobin was 8.8 grams per 100 ml. On examination one week after discharge the patient was asymptomatic with normal renal and hepatic function and improving anemia.

Discussion

Few isolations of Shigella dysenteriae type 1 had been recorded in the Western Hemisphere until the major epidemic of Shiga dysentery in Cen-

tral America in 1969.[3] An increase in the incidence of isolates of this organism in the United States has also been seen since 1969, mainly in travelers from Mexico and Central America.[6] However, several cases have been described in which no relevant travel history could be obtained, and spread within Los Angeles County was documented recently.[4] Assuming an incubation period of 5 to 7 days, in the present case the infection was most likely acquired in Mexico.

In the United States today, S. sonnei accounts for more than 80 percent of Shigella infections, with S. flexneri accounting for about 15 percent.[7] S. dysenteriae and S. boydii together have accounted for less than 1 percent. Shigella infection frequently presents as either a simple diarrheal illness or frank dysentery with high fever. However, the prominence of abdominal pain, nausea and vomiting, associated with minimal fever or toxicity early in the course distinguishes disease due to Shigella dysenteriae type 1 from that caused by other serotypes. Therefore, delays or confusion in diagnosis and treatment have been noted both in isolated cases and in epidemics of dysentery due to the Shiga bacillus.

Severe and prolonged gastrointestinal hemorrhage may be associated with extensive mucosal invasion and destruction.[8] In sporadic cases and during large epidemics, Shiga dysentery has been confused with ulcerative colitis and amebic dysentery. Several factors contribute to misdiagnosis. First, the Shiga bacillus has proved difficult to isolate with Salmonella-Shigella (SS) agar,[2] and often requires XLD, tergitol,[7] or MacConkey's agar for isolation. Second, this infection frequently coexists in regions endemic for Entamoeba histolytica, and the symptoms are mistaken for those of classical amebic dysentery. In the recent Central American epidemic, initial cases were thought to be secondary to Entamoeba histolytica, and trophozoites of E. histolytica were reported in the stools of some patients before the actual cause was established.[2] Finally, R-factor-mediated resistance to broad spectrum antibiotics commonly used in bacillary dysentery has led to the use of inappropriate antibiotic therapy. Virtually all isolates in Central America were resistant to chloramphenicol, tetracycline, and sulfathiazole, yet remained susceptible to ampicillin.[2]

During our patient's stay in hospital a pronounced granulocytic leukemoid reaction was noted. Leukocyte counts in blood have been variable in non-Shiga serotypes, with leukocytosis occurring more commonly than leukopenia. There is, however, a consistent and often pronounced shift to the left.[9] Our patient showed a dramatic fall in hematocrit, from 60 percent to 30 percent in 24 hours. The combination of intestinal bleeding, rehydration and hemolysis were all thought to play a role in this change. In addition, hematologic and hepatic dysfunction may have contributed to persistent lower intestinal hemorrhage. Thrombocytopenia is considered a rare complication.[9] The patient's thrombocytopenia was felt to be secondary to endotoxemia and sepsis. In addition, the morphologic abnormality of red blood cells associated with a positive protamine test[10] and prolonged prothrombin time and partial thromboplastin time suggested diffuse intravascular coagulation, and similarly this entity may have contributed to this patient's thrombocytopenia. Diffuse intravascular coagulation (DIC) was described in another recently reported case of S. dysenteriae type 1 disease in a five-year-old child.[11] In addition, a 14-month-old patient with a "hemolytic-uremic" syndrome has been described.[7]

Acute renal failure has been responsible for death in patients with acute shigellosis, although it is often difficult to separate renal failure due to infection from that due to profound dehydration. Both factors may have played a role in our patient's renal dysfunction, although acute tubular necrosis appeared to be a more likely explanation. In addition, diffuse intravascular coagulation has been associated with severe renal insufficiency.

Hepatic dysfunction has not been described frequently with shigellosis. In contrast to disease caused by the other Shigella serotypes, S. dysenteriae type 1 infection is frequently associated with bacteremia,[4] and alterations in renal and liver function and disturbances in coagulation are recognized complications of Gram-negative sepsis or endotoxemia. The frequent bacteremia and significant incidence of complications dictates systemic antibiotic therapy in infections due to S. dysenteriae, type 1. In contrast, antibiotic therapy in disease due to other Shigella serotypes has shown only modest benefit, at the expense of developing an alarmingly rapid increase in the incidence of resistant organisms.[14] Ampicillin is the drug of choice against the Shiga bacillus, particularly in view of R-factor-mediated resistance to chloramphenicol, streptomycin, sulfadiazine and tetracycline noted in the Central American epidemic.

Los Angeles County is currently an endemic

area for S. dysenteriae type 1. It is likely that more cases will appear in the United States, particularly in areas adjacent to Mexico. The insidious onset, the antibiotic resistance and the organism's potential for epidemic spread present a formidable problem. The association with episodes of prolonged intestinal hemorrhages, bacteremia, renal and hepatic dysfunction and coagulation disturbances further serves to emphasize the differentiation of disease produced by S. dysenteriae type 1 from that of other Shigella serotypes. The severity of the disease stresses the necessity of early recognition and initiation of appropriate aggressive antimicrobial and supportive therapy.

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Refer to: Carey WD, Brotman M: Clindamycin colitis—An emerging problem. West J Med 121:504-507, Dec 1974

Clindamycin Colitis
—An Emerging Problem

WILLIAM D. CAREY, MD
Rochester, Minnesota

MARTIN BROTMAN, MD
San Francisco, California

ANTIBIOTIC THERAPY is a two-edged sword: efficacy on one edge, toxicity on the other. The benefits of a new agent are widely disseminated soon after its introduction; the toxicity, even if severe, often takes months and years to become known.

Clindamycin is a seven-deoxy, seven-chloro derivative of lincomycin, an antibiotic elaborated by an actinomycete, Streptomyces lincolnensis.[1] Gastrointestinal side effects of lincomycin therapy have been reported extensively; it has long been recognized that diarrhea is a regular accompaniment of lincomycin given by mouth.[1-4] These episodes have usually been self-limited once the offending agent was removed. More recently a pseudomembranous enterocolitis, at times fatal, has been described.[5-7] Most documented cases followed lincomycin by mouth, but a few followed parenteral administration.

Clindamycin is currently being used more and more widely as an agent for anaerobic and Gram-positive aerobic infections. Although the manufacturer's package insert and advertising include notice that penicillins remain the drugs of choice for many Gram-positive upper respiratory tract infections, clindamycin is clearly being advocated for control of many of these infections. However, this drug, like its parent, produces a diarrheal illness and recently has been incriminated with increasing frequency as a cause of pseudomembranous enterocolitis.[8-14] The incidence of diarrhea and pseudomembranous colitis are said to be distinctly lower with clindamycin than with lincomycin, although substantiation of this lower toxicity is lacking.

This paper describes the first reported fatal case of clindamycin colitis and reviews previous cases documented in the literature.

Report of a Case

A 49-year-old Mexican woman was first admitted to the Pacific Medical Center in November, 1973, for hemodialysis following six months of weekly peritoneal dialysis elsewhere for idiopathic renal failure. Peritoneal dialysis had been uneventful except for episodic pleural effusion

From the Divisions of Nephrology and Gastroenterology, Presbyterian Hospital, San Francisco.

Submitted April 29, 1974.

Reprint requests to: M. Brotman, MD, 655 Sutter St., San Francisco, CA 94102.

thought to be secondary to dialysis. On one occasion it had been necessary to insert a tube into the left side of the chest for treatment of post-thoracentesis pneumothorax. There was history of abdominal complaints. One day before transfer, insertion of a new peritoneal dialysis catheter resulted in perforation of the transverse colon. On laparotomy a large amount of feco-purulent material was seen in the peritoneal cavity. A punctate hole in the transverse colon was closed and the abdominal cavity was thoroughly irrigated. Clindamycin was given intravenously, 600 mg three times a day for seven days. Kanamycin, 500 mg intramuscularly, was given for three doses. The postoperative course was uneventful. The patient was discharged on the 14th day, six days after cessation of clindamycin, with prescription of folic acid 1 mg daily and fluoxymesterone 10 mg daily.

The patient was readmitted five days later with complaint of abdominal pain, fever, and diarrhea, symptoms which had begun one day after discharge from hospital. At this time, the abdomen was soft, with increased non-obstructive bowel sounds and mild tenderness in the left lower quadrant. There were no masses or palpable organs. Digital rectal examination was unremarkable; sigmoidoscopy to 12 cm disclosed a uniformly erythematous, edematous, friable mucosa. Stool cultures were repeatedly negative for enteric pathogens; no ova or parasites were seen. Staphylococci were specifically sought but not found. Barium enema studies showed sigmoid diverticulosis without evidence of diverticulitis. The mucosal pattern was grossly abnormal throughout the colon and rectum, with pronounced edema and a "shaggy" mucosal pattern without definite ulcerations. An upper gastrointestinal roentgen series showed only edema of the duodenum. A diagnosis of probable clindamycin pancolitis was made and the patient was given prednisone, 40 mg daily, and psyllium hydrophilic mucilloid, 1 teaspoon twice daily. The gastrointestinal symptoms improved throughout the hospital course, and she was discharged, taking the above medications, after two revisions of her Scribner shunt. Prednisone was continued at this dosage thereafter except that methylprednisolone was given intravenously in the terminal stages of her illness.

She did well for several days at home and continued to have dialysis three times a week. However, recurrence of abdominal symptoms and the need for a new access to her circulatory system necessitated readmission after eight days. On physical examination no changes were noted. Laboratory data: glucose 245 mg, blood urea nitrogen 37 mg, total protein 5.4 grams, albumin 2.4 grams and total bilirubin 0.4 mg per 100 ml; alkaline phosphatase 152, lactic dehydrogenase 214 and serum glutamic oxalyic transaminase 54 international units; leukocytes 9,600 per cu mm, with 80 percent polymorphonuclear cells, 6 percent stab forms, 12 percent lymphocytes and 2 percent monocytes. The hematocrit was 24.1 percent and the hemogloblin content was 7.9 grams per 100 ml. Platelets were described as adequate. Urinalysis showed specific gravity of 1.010 and pH of 7.5; there were 3 white blood cells per high power field. Protein reaction was 2+. An x-ray film of the chest showed a small left pleural effusion with pleural thickening on the left which corresponded to the site of the previous chest tube placement.

Thrice weekly dialysis was continued with satisfactory control of uremia. An autologous saphenous vein graft was placed in the right arm. On proctoscopic examination the seventh hospital day, extensive involvement of the mucosa was seen, with elevated white irregular plaques on an erythematous background. Biopsy of one of these plaques showed mild chronic non-specific proctitis. Steroid and psyllium hydrophilic mucilloid therapy was continued. Frequent stools of small volume with considerable abdominal pain continued. Maintaining intravascular volume was difficult despite administration of large amounts of Plasmanate and salt-poor albumin. On the 16th hospital day, gastrointestinal bleeding was associated with disseminated intravascular coagulation (DIC). This was treated with blood, platelets and heparin, with only transient improvement. Selective celiac, superior and inferior mesenteric angiography disclosed no bleeding site. On procto-sigmoidoscopic examination the 19th hospital day there was no evidence of the plaques seen previously; the mucosa was denuded and had been replaced by granulation tissue.

Coagulase-negative staphylococcal septicemia (the primary source being an infected saphenous vein donor site) was treated with cephalothin, to which the organism demonstrated sensitivity by the pour plate method to a concentration of less than 15 mcg per ml. The patient received 12 grams of cephalothin the first day and four grams daily thereafter.

Life-threatening gastrointestinal bleeding (re-

quiring 12 units of blood) despite moderate improvement in coagulation studies led to laparotomy and colectomy with ileostomy. At this operation the entire abdomen was explored and no abscess or other pathologic process was found.

Grossly the resected colon was diffusely thickened; the mucosal surface was hyperemic and edematous, with adherent blood, beneath which were multiple elevated hemorrhagic lesions. Microscopically, there were focal hemorrhagic lesions involving the mucosa and submucosa, and vascular congestion. Fibrin thrombi were seen in a few arterioles. The overall picture was that of ischemic mucosal changes with variable amounts of reparative process. In some areas, clear mucin was seen overlying the mucosal surface, but no typical pseudomembrane was seen.

After colectomy, the patient improved for 24 hours but diffuse bleeding with DIC recurred. On the 28th hospital day, the abdomen was reexplored and there were no additional findings to explain the progressive deterioration. Death occurred on the 29th hospital day. There was no postmortem examination.

Comment

This case is similar to previously reported cases of clindamycin colitis.

The patient was female. In 11 of 15 previous case reports, the sex of the patient is mentioned; nine of these 11 were female. The reason for this apparent preponderence is obscure.

Our patient had received her last dose of clindamycin seven days before the development of abdominal symptoms. In many cases of lincomycin colitis and in at least two of the reported cases of clindamycin colitis, there were symptom-free intervals of varying length between cessation of antibiotic therapy and onset of symptoms.[7,8,14]

The route of administration of clindamycin was originally thought to be important in the pathogenesis of colitis, with disease following oral therapy in most early cases.[8,11] In this and other cases, disease followed intravenous administration.[9]

The course of the illness varies, from a week to several months of symptoms. The present case is unusual in that the course was inexorably downhill despite steroid therapy and subsequent colectomy.

The role of DIC in the patient's illness warrants comment. Her final admission to hospital was prompted by non-hemorrhagic gastrointestinal complaints. Coagulation studies did not suggest DIC until the last three weeks of her illness, five weeks after colitis began. Thus, while she died with DIC, it seems likely this was merely the final insult and not the precipitating event.

Severe protein loss and volume loss have been previously reported with this disease, and such losses were noted in our patient.[13] Although no quantitative data are available, protein-losing enteropathy is the most likely cause.

The severity of the mucosal insult varied throughout the course of our patient's illness. The initial lesion was that of a hemorrhagic friable, edematous mucosa. This was followed by development of creamy-white plaques on an erythematous background, which may be the hallmark lesion of this disorder.[7,15] Later, the mucosa was denuded and was replaced by granulation tissue; at colectomy, the changes were consistent with ischemic colitis.[16] These changes are described in previously reported patients but the changing appearance of the lesions has not been emphasized. The absence of a pseudomembrane at sigmoidoscopy therefore does not exclude the diagnosis. The radiographic features have recently been reported.[17]

Although oral glucocorticoid therapy has been used in many previous cases, its efficacy is unknown in the absence of controlled clinical trials. Our patient showed no response.

Although in other reported cases of clindamycin colitis the patient survived, many were critically ill. Scott et al reported seven cases associated with lincomycin; three of the patients died.[7] At least one of these deaths did not appear to be related to the underlying disease for which the patient received lincomycin, but to the sequelae of the colitis. Given the similarities of the drugs and the severity of the colitis produced by them, the risk of fatal colitis would appear significant.

In the case here reported, it is difficult to exclude other possible causes for the colitis. Hubbard has suggested alternate etiologic possibilities in both lincomycin and clindamycin colitis.[18] Uremia has been reported as a cause of both pseudomembranous colitis and ischemic colitis. We are not aware of such reports in patients receiving adequate hemodialysis.[15,16] Postoperative pseudomembranous enterocolitis has been described, particularly following intra-abdominal operations.[19] However, the onset of symptoms is usually earlier, averaging three and a half days after operation, compared with 15 days in the present case. Additionally, our patient received

three doses of kanamycin and it is at least possible that this drug, or a combination of the two drugs, was responsible for the severe colitis. Kanamycin is removed by hemodialysis, hence did not accumulate. Moreover, colitis with kanamycin has not been previously described. Clindamycin remains the most likely etiologic factor in this case.

The pathogenesis of the colitis with clindamycin is unknown. The parent drug, lincomycin, is thought by some investigators to exert its gastrointestinal toxicity by virtue of its relatively poor absorption (20 to 30 percent) and resultant high concentration in the large bowel. Here, either by altering the flora or by a direct toxic effect on the mucosal cells themselves, the drug is thought to cause diarrhea and sometimes pseudomembranous enterocolitis. The observation that lincomycin can cause this syndrome when given parenterally[14] is not entirely at variance with these mechanisms, since the bile is an important excretory route of lincomycin and its metabolites.

When clindamycin is given orally, absorption is about 90 percent, but excretory routes are similar to those of lincomycin. Thus, although direct toxic effect due to the presence of unabsorbed clindamycin in the large bowel is unlikely, metabolic degradation products excreted in the bile could cause toxic concentrations to be present in the gut.

The proposed mechanisms must be considered entirely spectulative at this time and do not explain why gastrointestinal toxicity develops in only a fraction of patients who are given these drugs.

Conclusion

Clindamycin has an attractive spectrum of activity against Gram-positive cocci, including penicillinase-producing straphylococci, and against Gram-negative anaerobes, including those usually resistant to penicillin (for example, Bacteroides fragilis). Colitis, which may be fulminant and life-threatening, has now been reported in at least 16 cases. The incidence of this complication is unknown, one estimate being 1 per 100,000 cases.[18] We suspect the incidence of mild to moderate colitis to be much higher. A controlled prospective trial, conceivably as a large-scale cooperative study, is the only way to establish the magnitude of the problem. This may be important to carry out, considering the frequency with which anaerobic infections are being found. When penicillin-resistant anaerobes are suspected or found, clindamycin or chloramphenicol is usually selected. The *relative* risk of toxicity with these drugs is unknown.

The role of clindamycin in antibacterial therapy remains unclear. It is preferable to use another drug for most Gram-positives infections, especially for minor infections and most skin and upper respiratory infections. Clindamycin should be reserved for serious infections likely to be caused by Bacteroides fragilis or other penicillin-resistant anaerobes.

Summary

A case of fatal pancolitis following seven days of parenteral clindamycin therapy for colon perforation is presented. Fifteen previously reported cases of "clindamycin-colitis" are reviewed. The sex incidence (female predominance) and occurrence following parenteral *or* oral administration are noted. The clinical course and proctosigmoidoscopic findings are widely varied. Glucocorticoid therapy is not of proven efficacy. The need for additional information regarding the incidence of this side effect of clindamycin is evident.

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LETTERS *to the Editor*

Vitamin D and Calcium Homeostasis

To the Editor: We are writing to correct some of the comments made by Dr. H. F. DeLuca in his editorial [Impact of recent findings concerning vitamin D metabolism on clinical medicine. West J Med 121:64-65, Jul 1974] concerning our review article "Metabolism and Action of the Hormone Vitamin D—Its Relation to Diseases of Calcium Homeostasis" [West J Med 121:22-44, Jul 1974] which also appeared in The Western Journal of Medicine. It is incorrect for DeLuca to state that "vitamin D may be classified as a steroid only because it is derived from a precursor which possesses a steroid nucleus [and that] the resemblance of 1,25-$(OH)_2$-D_3 to a steroid is vague at best." The precursor 7-dehydrocholesterol and both cholecalciferol [vitamin D_3 or technically 9,10-secocholesta-5,7,10(19)-triene-3β-ol] and 1,-25-$(OH)_2$-D_3 [technically 9,10-secocholesta-5,7,-10(19)-triene-1α,3β,25-triol] are all steroids according to the official nomenclature rules of the International Union of Pure and Applied Chemistry (IUPAC).[1] In particular, cholecalciferol and all its known metabolites are "seco" steroids. Seco steroids occur by definition in steroids with the characteristic cyclopentanoperhydrophenanthrene ring structure when "ring fission with addition of a hydrogen atom at each terminal group thus created occurs. These new compounds are indicated by the prefix 'seco,' the original steroid numbering being retained." [See rule 7.4; reference 1.] In fact, the example of a seco steroid given in reference 1 is cholecalciferol.

We certainly stoutly maintain that the mode of action of 1,25-$(OH)_2$-D_3 is analogous to that of many other classical steroids. The reader is directed to the numerous papers published by the laboratories of Lawson and Kodicek, Wasserman, and Norman for a full elaboration of the argument. There is ample documentation of the renal production and distal interaction and localization in the nucleus of the intestinal cells of 1α,25-$(OH)_2$-D_3.[2] This nuclear localization of 1α,25-$(OH)_2$-D_3 results in the *de novo* synthesis of a m-RNA[3] which codes for a protein unique to the presence of vitamin D and its metabolite, calcium binding protein.[4] Certainly these observations qualify 1α,25-$(OH)_2$-D_3 as being a steroid hormone of status which is of equal legitimacy to that of estradiol, progesterone, testosterone, etc. However, it is obviously an important problem for all steroids, including 1α,25-$(OH)_2$-D_3, to know whether *all* the biological actions occur as a consequence of nuclear interaction. Any reservations DeLuca has in this respect are, of course, equally shared by all workers concerned with the mechanism of action of steroids.

Anthony W. Norman, ph d
University of California, Riverside

Jack W. Coburn, md
David Hartenbower, md
Veterans Administration Wadsworth Hospital Center Los Angeles

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Semi-Retired Physicians

To the Editor: I have a problem, which I probably share with hundreds of other semi-retired California physicians like myself.

I closed my office three years ago—I am now 75 years of age. My medical work is now mostly done in convalescent hospitals, but not as an employed physician. The number of patients I examine and treat may vary between 30 and 40 a month, which means a medial gross income of just several hundred dollars.

In order to keep up with medical education, especially in Category 1, I am forced to go to the Stanford and San Francisco areas for lectures with

high registration fees, besides expensive hotel or motel lodgings.

May I suggest that unemployed semi-retired physicians might be given a chance for reduced fees for attendance at symposia and lectures by presenting a "Senior Physician's pass" issued by the CMA.

REINHARD J. BACHRACH, MD
Salinas, California

EDITOR'S COMMENT: Your suggestion, which has been made by others as well, has been considered by CMA's Scientific Board. Recently the CMA Council approved the Board's recommendation that all retired CMA members be allowed to attend CMA-sponsored Continuing Medical Education programs, including Postgraduate Institutes, at no charge. The Scientific Board is also encouraging medical schools and hospitals accredited for continuing medical education to do likewise.

The Battered Child

TO THE EDITOR: The excellent article [by Richard J. Kohlman] "Malpractice Liability for Failing to Report Child Abuse" [West J Med 121:244-248, Sep 1974] failed to include an extremely important aspect in the reporting mechanism that doctors apparently have too little view of: the failure of the police authorities to continue to follow through in the cases that we physicians *do* report.

I became personally aware of this problem nearly 18 months ago (the first of the four battered children I saw in my practice alone during this period of time); that particular case involved a foul-up among authorities. District Attorney Joseph Busch began his letter to me: "Please rest assured that the obstacles placed in the path of justice by the respective lumbering bureaucracies involved have finally been surmounted."

But—they were not. About a month ago, I reported a case involving a mother who was on the telephone to me at that time (admitting that she had beaten her son, possibly causing a broken nose, and at times could not control her emotions). The police went out, accepted her story that she accidentally hit her son on the face, did not take the child for medical evaluation and did not report further (as they are required to do by Penal Code:11161.5: "the police are to forward the written report to the State Bureau of Criminal Identification and Investigation. This Bureau in turn must communicate back to the local reporting agency and the Juvenile Probation Department any information . . . "). The *police,* in this situation, did not follow through on my emergency reporting of an on-going child-battering as prescribed by law. Within a two-week period I had two additional cases of battered children (suspected, as in the earlier case) that the police had investigated, and not taken for medical evaluation or reported further as regulations insist. My personal communications with the law agencies involved corrected these situations, and the watch commanders promised further instruction of the officers in their command.

My point is that just as we physicians are required by law to, in cases of possible-battered children, "report such fact by telephone and in writing to the head of the police department of the city or county . . . and to the local Juvenile Probation Department" (Section 11161.5 of the Penal Code), the police also have duties under the same law. I question whether enough of our officers are aware of this, as exemplified by my experience, and by an earlier case in which the city of Arroyo Grande lost a suit because its police chief had not notified the Department of Social Welfare and had taken no further action . . . the child later was re-battered.

BURTON SOKOLOFF, MD
Canoga Park, California

Refer to: Thomas AN: Penetrating thoracic trauma (Trauma Rounds). West J Med 121:510-513, Dec 1974

Trauma Rounds

Chief Discussant
ARTHUR N. THOMAS, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Penetrating Thoracic Trauma

TED PREIS, MD:* The case for discussion today is that of a 23-year-old white man who was brought into the emergency room 15 minutes after receiving a stab wound in the right hemithorax. The patient was awake but the sensorium was depressed. The skin was cool to the touch and the blood pressure was 70 systolic. On physical examination, a stab wound three inches in length was noted at the level of the fifth intercostal space in the right parasternal line. Breath sounds were absent over the right chest; there were coarse breath sounds on the left. The abdomen was scaphoid without tenderness.

Two cutdowns were made and 1,500 ml of saline was administered. The blood pressure rose within five minutes to 120/80 mm of mercury, with a pulse of 100. Chest tubes were placed in both the right and left pleural spaces. The right drained 500 ml of fresh blood. An x-ray film of the chest was taken in route to the operating room and showed some opacity of the right hemithorax and a small pneumothorax.

DONALD D. TRUNKEY, MD:† *Why was this patient taken immediately to the operating room rather than observed further?*

DR. ROBERT BUSH, MD:‡ The patient had had an extensive loss of blood at the scene of the accident. After initial drainage from the chest had ceased, there still remained a question as to whether there was bleeding into the abdominal cavity. Although the abdomen was benign to physical examination, we were not entirely satisfied with the fact that the blood loss was entirely from the chest. Therefore, we planned to carry out an exporatory laparotomy.

DR. TRUNKEY: *Dr. Thomas, using this case as a starting point for discussion, would you outline the principles of managing penetrating injuries of the chest?*

ARTHUR N. THOMAS, MD:§ *Was the patient's venous pressure recorded during resuscitation? If so, this would narrow the differential diagnosis to a considerable extent.*

DR. BUSH: At the time of admission, the first thing I did was examine the neck veins and found that they were collapsed. After the upper extremity cutdown was made, we could get a central venous pressure and this was never more than 2 cm of water.

DR. THOMAS: If a patient's neck veins are distended, the most common causes are tension pneumothorax and pericardial tamponade. Recently we have come to recognize that air embolism can occur after penetrating chest injuries of this type and this can decrease the ability of the heart to function as a pump and result in venous congestion, particularly when a fluid load is given.

Most penetrating injuries of the chest do not require thoracotomy. Approximately 95 percent of knife wounds and 80 percent of gunshot wounds can be managed conservatively. The lung is capable of tamponading injury to parenchymal vessels and most continued bleeding is from vessels

*Trauma Service Intern.

†Chief of Surgery, Mission Emergency Hospital and Assistant Professor of Surgery, University of California, San Francisco.

‡Chief Resident, Trauma Service.

Supported in part by NIH Grant GM 18470 and the Northern California Trauma Committee, American College of Surgeons.

Reprint requests to: D. D. Trunkey, MD, Department of Surgery, San Francisco General Hospital, San Francsco, CA 94110.

§Chief of Thoracic Surgery, San Francisco General Hospital, and Associate Professor of Surgery, University of California, San Francisco.

of the chest wall. When there is major hilar or mediastinal vascular injury, immediate fatality is a rule so these rarely present as clinical problems statistically.

The main problem initially is to assess the extent of intra-abdominal injury because far more patients with penetrating thoracic injuries require laparotomy rather than thoracotomy. Injuries below the sixth intercostal interspace very frequently enter the abdominal cavity via the diaphragm. A patient with a lower thoracic injury must be considered to have a thoraco-abdominal injury and attention should be directed toward the abdomen as well as the chest. The status of the chest bleeding is assessed by prompt placement of a chest tube and by obtaining x-ray films of the chest. Continued unexplained massive blood loss (such as that not visible in x-ray studies of the chest or from chest tube drainage) implies intra-abdominal hemorrhage and prompt exploratory laparotomy is indicated. Injuries above the sixth interspace are less likely to penetrate the abdomen but still may occasionally do so. We believe that all penetrating wounds of the abdomen should be explored because of the possibility of hollow viscus injury even in the absence of bleeding. All lacerations of the diaphragm should be repaired at the same time, whether a laparotomy or thoracotomy is done to prevent future herniation of abdominal viscera into the chest.

The initial assessment of a patient with a chest injury includes assessing oxygenation and looking for evidence of hemopneumothorax. When the pleural space has been obviously violated, a chest tube should promptly be inserted whether or not the patient's condition is stabile. When hemothorax is suspected or present, the tube is placed in the mid-axillary line somewhere near the sixth interspace. After making an incision through the skin and subcutaneous tissue, a clamp is inserted through the chest wall to allow passage of the surgeon's finger. Digital exploration of the proposed tract for the chest tube will pick up unsuspected pleural adhesions, permit the early recognition of blood and let the lung collapse away from the chest tube so it will enter the pleural space. A number of catastrophes relate to the fact that the chest tube slides under the thoracic musculature without entering the pleural cavity and delayed recognition of pleural blood loss or a tension pneumothorax occurs. If the only goal is to re-expand a collapsed lung from pneumothorax, the chest tube should be placed anteriorly in the second intercostal space in the mid-clavicular line. In both instances a tube of adequate design and dimensions such as a 36 angled Argyle should be used.

The major indication for immediate thoractomy is failure of the patient to promptly respond to resuscitation. The most common reason for this is major hemorrhage. Despite prompt intravenous fluid replacement, blood pressure and perfusion cannot be restored to normal levels. The second most frequent indication for immediate thoracotomy is pericardial tamponade. Massive continuous leakage of the air from injuries to the tracheobronchial tree represents a third indication for immediate thoracotomy.

DR. TRUNKEY: *Dr. Thomas, what amount of hemothorax is considered to be an indication for thoracotomy?*

DR. THOMAS: The amount of bleeding indicating the need for thoracotomy is relative to the rate of bleeding. First, there may not be a relationship between the need for thoracotomy and the initial amount of blood removed from the chest cavity. However, if the amount of pleural blood is massive, and the interval between the injury and initial treatment is brief, the assumption should be that a major vascular injury has occurred. But ordinarily it is the rate, not the volume of hemorrhage that determines unacceptable levels of bleeding and is an indication for thoracotomy.

The patient's response to resuscitation is most important to observe. When there is shock and vascular instability, or the patient responds only briefly to resuscitation, an immediate thoracotomy is indicated. In many cases, the patient will remain stabile after adequate volume replacement, and can be safely observed. In most instances, bleeding amounting to 500 ml per hour or greater during the first hour is an absolute indication for thoracotomy. When bleeding is at this rate, reassessment or output at five to ten minute intervals may be necessary. On the other hand, if the loss of blood is less than 100 ml per hour, conservative management is generally indicated because one expects that the bleeding will cease spontaneously. When bleeding is at a level of 200 ml per hour or more during three hours of observation, an unacceptable rate of hemorrhage exists and thoracotomy should be done. Blood loss at a rate of 100 and 200 ml per hour can be tolerated for a number of hours and observation is justified pro-

vided volume loss is progressively decreasing. If observation for several hours is decided upon, periodic chest x-ray films should be taken to rule out progressive accumulation of blood within the chest.

DR. TRUNKEY: *What would be your indication for thoracotomy in the emergency room?*

DR. THOMAS: Immediate thoracotomy in the emergency room is necessary to resuscitate some patients who enter the hospital in extremis and do not promptly respond to initial attempts at resuscitation. In the delay caused by taking such a patient to the operating room, the opportunity to save him might be lost. Immediate emergency room thoracotomy is done to determine diagnosis, control hemorrhage, stop a major air leak from bronchial injury or to evacuate pericardial tamponade. A thoracotomy done with relatively nonsterile technique is surprisingly well tolerated and wound infections occur less often than might be expected. In the past 50 or 60 of these thoracotomies, I can only recall one major wound infection. When the chest is opened, if massive hilar hemorrhage is encountered, a hand or vascular clamp can be placed across the hilum of the lung to curtail bleeding temporarily, until the patient is transported to the operating room.

A PHYSICIAN: *When there is a penetrating injury of the chest, would you obtain an x-ray film of the chest before inserting a chest tube, or would you insert a chest tube first?*

DR. THOMAS: If the patient is stabile and doing well, a chest x-ray study should be obtained before inserting a chest tube. Just how accessible x-ray facilities are will have a bearing on whether it is safer to put in a chest tube without previous x-ray studies, than to risk the possible deterioration of a patient.

An obvious indication for chest tube placement (such as a pneumothorax, chest bleeding or sucking chest wounds) make the decision for prompt insertion of a chest tube easy.

A PHYSICIAN: *Would you ever put the chest tube through the wound?*

DR. THOMAS: No, I would not do that. The wound is presumably contaminated, and the placement of a chest tube through that wound would further contaminate the pleural space. In addition, the location of the wound is often not optimal for the placement of a chest tube, or may be located so as to interfere with the location of an incision to explore the chest.

DR. TRUNKEY: *Dr. Bush, would you tell us what you found in treating this patient, and how the patient has done since operation?*

DR. BUSH: We took the patient to the operating room and explored the stab wound locally. As we palpated this wound, it did not seem to penetrate the diaphragm or pericardium. We proceeded with a limited laparotomy making a small incision in the epigastrium. It was seen that there was no penetration of the abdominal cavity. By the time this wound was closed, 500 ml of blood had welled up from the chest wound so that it appeared that bleeding from the chest wound was going to continue at the previously defined unacceptable rate. The patient was positioned for an anteriolateral thoracotomy and this was carried out through the fifth interspace. The wound extended through lung substance, into the hilum where a large pulmonary vein to the upper lobe had been injured. A vascular clamp was placed across the hilum, the upper lobe dissected out and an upper lobectomy done. This controlled the hemorrhage; the lower lobe was re-expanded. The stab wound was sutured closed pleurally and the subcutaneous portion of the wound left open. The thoracotomy incision was closed, leaving the chest tube in place. The post-operative course was benign and at present the lung is fully expanded and fills the right hemithorax except for a small cap of air at the apex of the chest cavity.

F. WILLIAM BLAISDELL, MD:* *Dr. Thomas, do you have any tricks for controlling hilar bleeding such as occurred in this case?*

DR. THOMAS: No, usually the application of fingers or vascular clamp across the hilum will control things satisfactorily if all the bleeding is into the pleural space. Exposure of the laceration may be difficult if partially covered by the occluding clamp. Sometimes it may be of value to open the pericardium and control the vessels to the lung through this route. If there is a major associated cardiac injury, this may be controlled by inserting a finger into the cardiac wound. Rarely, fibrillating the heart and carrying out temporary cardiac

*Chief of Surgical Service, San Francisco General Hospital; Professor of Surgery, University of California, San Francisco.

arrest may permit a dry field long enough to expose and repair the critical area.

I'd like to ask Dr. Lim to comment on the roll of autotransfusion in the management of these patients.

ROBERT LIM, MD:* We have established a routine set-up for autotransfusion in the emergency room. Our chest bottles are kept sterilized in the emergency room and citrate-phosphate-dextrose (CPD) anticoagulant is added to these bottles after they have been prepared. Automatically then, when a chest tube is connected to water seal drainage, the first or dry bottle contains anticoagulant and the blood removed is automatically anticoagulated and can be given back to the patient. We have found this is a satisfactory method to re-expand the patient's blood volume, particularly if bleeding is massive and there is a delay in obtaining blood from the blood bank. The blood is appropriately matched, the chest cavity is a clean body space and the blood can be used to advantage. The blood, however, despite the addition of anticoagulant has been defibrinated and all platelets removed so that it is not effective for hemostasis. For this reason, we do not like to give more than 1,500 or 2,000 ml. The blood we are giving from this type of autotransfusion essentially consists of a plasma expander and red cells.

DR. BLAISDELL: *What about autotransfusion after abdominal injuries?*

DR. LIM: Abdominal injuries are a different matter. In these circumstances there is often an associated injury of the bowel and the emergency aspect of a major intra-abdominal vascular injury is such that one rarely has an opportunity to rule out potential for contamination while dealing with major ongoing hemorrhage.

It should be emphasized that autotransfusion is no substitute for prompt definitive surgical operation. If there is bleeding at such a rate as to require transfusion to keep a patient out of shock, immediate operation is indicated. Autotransfusion may be of greater value in more remote localities where access to a blood bank is not as immediate. Under these circumstances the emergency room in the hospital would be well advised to consider saving all blood aspirated whether from the chest or the abdominal cavity. Initially, Ringers lactate or crystalloid can be used for resuscitation, and later after the full nature of the patient's injuries have been determined, the saved anticoagulated blood can be reinfused. We advise placing good filters in the lines. One of the newer micropore filters would be most appropriate.

DR. TRUNKEY: *Dr. Thomas, I have one final question relative to penetrating chest trauma. You have identified the syndrome of air embolism, would you comment on this?*

DR. THOMAS: Air embolism can occur in any patient with a penetrating injury of the chest. The patient often presents with hypotension, yet the degree of shock seems out of proportion to the blood loss observed. During or after resuscitation, the patient may continue to suffer from power failure or diminished cardiac output, but pericardial tamponade or tension pneumothorax are not found to explain this. Air embolism has been found in 11 of our patients to date. It results when laceration of the lung produces a bronchial pulmonary venous fistula. Air leaves the bronchial tree and is shunted directly into a pulmonary vein. It enters the left heart and is pumped from there into the systemic circulation. In shock, the pulmonary veins have a very low pressure and in addition, many of these patients often have positive pressure ventilation instituted which increases the differential pressure between the bronchus and the pulmonary vein. While air is well tolerated on the right side of the heart, even small increments of air in certain critical areas of systemic circulation may produce catastrophe. As little as 0.5 ml of air in the anterior descending coronary artery may produce a fatal cardiac arrythmia. These patients may also manifest evidence of cerebral air embolism with dilated pupils and depressed sensorium.

The essentials for treatment of patients with arterial air embolism following a lung injury are to remove the air from the left ventricle and root of the aorta and prevent further air entry into the circulation by isolating the injured lung between clamps. It may be necessary to manually compress the heart, use drugs to stimulate cardiac action or temporarily occlude the thoracic aorta distal to the subclavian artery as a means of increasing coronary artery pressure to levels that could drive air trapped in coronary circulation through the capillary network. General measures include putting the head down to minimize cerebral air embolism and applying the usual treatment for shock.

*Associate Professor of Surgery, University of California, San Francisco.

Refer to: Geyman JP, Brown TC: A developing regional network residency program in family practice (Medical Education). West J Med 121:514-520, Dec 1974

A Developing Regional Network Residency Program in Family Practice

JOHN P. GEYMAN, MD, *and* THOMAS C. BROWN, PhD, *Davis, California*

IN THE FIELD OF MEDICAL EDUCATION, the last ten years have seen growing interest in several new directions. Major among these are decentralization of medical education; increased involvement of community hospitals and practicing physicians in the educational process; development of medical education as a continuum involving undergraduate, graduate and postgraduate phases; and a shifting emphasis toward training of primary care physicians.[1-6] One of the important events in recent years has been the rapid emergence of family practice as a major force in medical education and practice. Since its inception as a specialty in 1969, there has been a rapid proliferation of family practice residency programs throughout the country, a resurgence of interest among medical students in this field and the organization of departments or divisions of family practice in a majority of the nation's medical schools.

Educational programs in family practice lend themselves particularly well to being based in communities and represent an important opportunity to decentralize medical education and expand the role of the university regionally. This article describes the rationale, goals, components and advantages of such a regional approach to medical education being taken at the University of California, Davis.

From the Department of Family Practice, University of California, Davis, School of Medicine.

Submitted, revised, September 13, 1974.

Reprint requests to: J. P. Geyman, MD, Department of Family Practice, University of California, Davis, School of Medicine, Davis, CA 95616.

Rationale for Regional Network Approach

A clinical and teaching base for family practice at the university medical center is vital for several important reasons. There is a need for visibility of family practice among medical students on the same basis as other clinical specialties in the medical school. Medical students must see credible role models of family physicians throughout their undergraduate medical education. Educational programs in family practice must be developed as a continuum starting with the first day of medical school for the freshman medical student, through the undergraduate period, graduate training and postgraduate medical education. It is important that family practice develop in association with other clinical specialties instead of in isolaton from them. The extensive resources of the university base can be mobilized in the design, implementation and evaluation of educational programs in family practice. In addition, the university base provides an increased potential for research, testing and evaluation of improved methods of patient care and teaching.

Although a university base for family practice is considered essential, it is fully recognized that it is both logical and appropriate that many of the educational programs in family practice be carried out in various community settings where the spectrum of illness more closely approximates that which the future family physician will regularly encounter in practice. The development of affiliated family practice residency programs in outly-

ing community hospitals represents an effective approach to decentralizing family practice education at all levels. Each such residency program necessarily involves the active participation of family physicians and other specialists from the community. In this way, residents can train in settings similar to that of their future practice. The development of university affiliated residency programs also creates opportunities for undergraduate medical students to take elective preceptorships and clerkships in these outlying communities. These programs involve more meaningful and accessible opportunities for the continuing medical education of practicing physicans in such communities through their direct participation as teachers and through other, indirect associations with the residency training programs.

Based on the precept that family practice residency training should be patterned as closely as possible on the realities of the family physician's practice, the well-developed network of affiliated programs should include educational models for rural, suburban and urban practice. It is felt that locating these affiliated programs in areas with a physician shortage can effectively increase physician manpower in such areas, since it has been shown that physicians often locate their practices within 100 miles of the community where they completed their residency training period.[7,8] In Ventura County, California, for example, over 50 percent of family physicians in active practice graduated from the family practice residency program at Ventura General Hospital (previously a general practice residency); 37 percent of this program's graduates remained in Ventura County.

Goals of Regional Network

Based on the rationale described, the Department of Family Practice at the University of California, Davis, School of Medicine has been working since 1972 to develop a regional network residency program in central and northern California. With the help of supplemental funding from the W. K. Kellogg Foundation, excellent progress has been made. A strong university-based program has been established at the University of California, Davis, Sacramento Medical Center, where there are now 21 residents in training. The second residency program within the network was begun at San Joaquin General Hospital in Stockton in July 1973, and there are now 11 residents in training there. The third component program began operation at Merced Community Medical Center in Merced in July 1974, and there are presently three residents in training in this affiliated program. With the support of supplemental state funding (through Song-Brown legislation), it is anticipated that additional programs will be started on the Davis campus and in Redding hospitals in July 1975. There are now 35 residents in training within the network residency program, with a projected increase to 67 residents during the 1975-1976 year. Other potential affiliated programs are being considered for future inclusion within the regional network.

The overall goals of the University of California, Davis, Family Practice Residency Program are threefold:

1. To train family physicians able to respond to changing health care needs of central and northern California and adjacent areas.
2. To develop innovative models for the teaching and practice of family medicine in varied settings.
3. To develop a model for the optimal partnership relationship between the university and affiliated community hospital programs which should improve the quality of family practice residency training.

Objectives of the network program in University of California, Davis, Affiliated Hospitals for Family Practice may be stated more specifically.

1. To provide residents with opportunities to train in a variety of settings:

- Rural, suburban or urban areas.
- Patient populations of different compositions.
- Partnership, group and pre-paid capitation group practice arrangements.
- University medical center and community hospitals of different sizes.
- Health care teams of varied types.

2. To further define educational objectives in order to make them most effective for family practice residency training and to refine evaluation techniques.
3. To integrate family practice residency training with family nurse practitioners' training where possible.
4. To encourage group practice by future family physicians, involving family practice teams.
5. To develop an active research program in family practice.
6. To evaluate and improve the network residency program through a continuing assessment

of medical care needs in the region including longitudinal follow-up of practice settings and practice patterns of program graduates.

Components of Network Program

Program Administration

Regular meetings are held involving the director of the University of California, Davis, Family Practice Residency Program and program directors from each affiliated hospital. An active interchange of University-based faculty has been developed in which faculty from the Department of Family Practice visits each affiliated program weekly. These contacts provide continuity to the process of planning, operating and evaluating the overall program. It is expected that each affiliated program will develop its own unique strengths and innovations. The pooling of ideas and experience within the network should contribute to a dynamic, high quality program, which essentially can be viewed as a "family" of affiliated family practice residency programs.

Each affiliated residency program necessarily depends heavily upon the active involvement of practicing physicians in the training program. Teaching physicians in each of the component programs are jointly selected by the director of the affiliated program and director of the network program. Criteria for the selection of a teaching physician are professional reputation as a clinician, capacity to relate constructively with residents, motivation and enthusiasm as a teacher, interest and commitment to the goals of the residency training program, established habits of continuing medical education and willingness to adapt practice demands to allow sufficient time to resident teaching. Based upon their demonstrated performance as teachers, the program director will nominate selected physicians for clinical appointments in the Department of Family Practice at the University of California, Davis, School of Medicine. Members of the clinical faculty are expected to contribute a minimum of 50 hours each year to resident teaching, to attend all teacher development workshops, to use the problem-oriented record and audit techniques as teaching tools and to take an active part in teaching conferences and evaluation of resident performance.

Formal affiliation agreements have been developed between the University of California, Davis, School of Medicine and each affiliated community hospital. These affiliation agreements delineate the overall responsibilities of the University and the community hospital; responsibilities for payment of resident salaries and other program costs; the process by which resident applicants are selected and responsibilities for the planning, design, operation and evaluation of the residency training program.

Competency-Based Curriculum

At the heart of the teaching program and its evaluation is the concept of a competency-based curriculum.[9] The assumption is commonly made in graduate medical education that intended educational outcomes for residents can be derived from standard clinical experiences over arbitrary periods of time. Instead, we are attempting to write competency statements for the breadth of family practice which are sufficiently specific to allow measurement of individual resident progress so that each resident can best use the educational opportunities available within the three-year residency experience. A criterion group has been established consisting of twelve family physicians, equally balanced between full-time teachers and practicing family physicians. This group is now working to write specific clinical competency statements which are directly related to those definitive capabilities required of program graduates in their anticipated future practice setting.

The curriculum of the network residency program includes three basic approaches: block rotations, modified block rotations and longitudinal learning experiences. Block rotations are periods of time devoted primarily to one major clinical discipline, such as a clinical rotation on the medicine service for four months. Modified block rotations are block rotations which include other concurrent learning experiences, such as supplemental training in other specialty clinics or preceptorships. Longitudinal learning experiences are provided over an extended period of time on an intermittent basis, such as training in counseling techniques. Certain components of the curriculum are provided more effectively through one of these three approaches.

The foundation for the entire program is the resident's experience in the model family practice unit. This is his home base during the three-year residency, where he is responsible for the care of an increasing number of families under the close supervision of the faculty. The emphasis during early training in the residency program is on hospital-based training in all the major clinical serv-

ices relevant to family practice. In the later phases of training, residents practice more extensively in the model family practice units and the emphasis shifts to ambulatory care—with approximately an even balance between inpatient and outpatient care over the entire training period. Sufficient elective time is provided in the third year of the program for each resident to specifically prepare for the particular needs of his own anticipated practice setting.

We have adapted the curriculum and size of each component program within the network to the educational and clinical resources available within each community. The Sacramento Medical Center and San Joaquin General Hospital programs are based in hospitals of 500 and 220 beds, respectively, each with a substantial number of full-time teaching physicians and a sizable number of residents in other specialties. In these cases, most experiences of the full three-year residency program can be provided within each hospital.

In the case of affiliated programs in smaller communities with less extensive educational and clinical resources, the entire first residency year, together with three months of medicine selective rotations during the second and third years, are provided at Sacramento Medical Center. The Merced program, for example, has sufficient teaching resources to support the training of second and third year family practice residents (four in each year). There is currently a total of 42 teaching physicians participating in the program at Merced Community Medical Center (160 beds). This total comprises 12 in family practice, 6 in internal medicine, 2 in pediatrics, 4 in obstetrics-gynecology, 12 in surgery (including surgical subspecialties), 1 in neurology, 1 in psychiatry, 1 in radiology and 1 in pathology. Although the curriculum within any component program of the network varies with available resources and local circumstances, similar competency-based objectives for family practice apply throughout the network program in University of California, Davis, Affiliated Hospitals for Family Practice.

Visiting Professor Program

An active visiting professor program is being carried out for all affiliated programs, involving faculty from the Department of Family Practice, from other clinical and basic science departments in the School of Medicine and from other departments in the university. This program is usually conducted biweekly, with the fields and subjects selected so as to best supplement the educational resources available to each affiliated program.

The format of the visiting professor program necessarily varies with the consultant's field of interest and expertise, but usually includes a didactic presentation, as well as an informal seminar—including case presentations by the residents. Consultants may make rounds seeing patients in the hospital and will often audit selected charts in a teaching seminar. Part of the visiting professor's presentation is scheduled during the noon hour, a time which is the most convenient for practicing physicians in the community.

Visiting family practice faculty assist the director of the affiliated program with resident evaluation, audit techniques and teaching in the model family practice unit—and help to troubleshoot problems in the training program. They also help to coordinate the needs of the affiliated program for supplemental teaching through the visiting professor program and self-instructional materials.

Network Teaching Bank

A network teaching bank of self-instructional materials has been developed including over 500 multi-media self-instructional units representing all clinical fields related to family practice. Particular stress has been placed on the use of media which are portable and easily maintained, and which will facilitate individualized learning by residents. Learning carrels have been established in each affiliated residency site in the program's model family practice unit for the use of videocassette, tape-slide and other self-instructional media.

A network teaching bank should be of value to residents, practicing family physicians, medical students and family nurse practitioners. Within the residency program, some self-instructional materials are keyed to supplement the visiting professor program, while others are keyed to specific clinical rotations at each level of resident training. Selected self-instructional materials are placed in each affiliated community hospital for one week before and after each visiting professor program. A basic set of self-instructional units has been identified in all major clinical areas to directly support clinical rotations on medicine (first and second years), surgery, obstetrics-gynecology, pediatrics and psychiatry. These self-instructional

media are in constant use and are available in each affiliated hospital for one month out of every quarter. To date, residents have made excellent use of these materials. Additional self-instructional materials are shared within the network program as they are needed.

Network Self-Assessment Center

A network self-assessment center has been developed on the Davis campus in an effort to better monitor and improve the quality of resident training in all affiliated hospitals. This part of the network program includes several major components:

- Data bank of examination questions.
- An annual self-assessment examination keyed to resident training, together with follow-up practice examinations in specific areas.
- Learning modules of packaged self-instructional units including pre- and post-testing components.
- Performance files for each resident, including clinical rating forms completed regularly by supervising faculty—as well as completed self-assessment and examination materials and medical record audit data.

A criterion-referenced, diagnostic self-assessment examination has been developed which incorporates testing techniques used by the American Board of Family Practice. This examination is given annually to all residents within the network. This has allowed profiling of individual resident performance in all major clinical areas, as well as in subspecialty areas. Residents are encouraged to formulate individualized learning approaches to specific areas of need through such resources as the network teaching bank, specific modification of clinical rotations, selectives, electives and follow-up examinations. The confidentiality of individual resident profiles is closely maintained consistent with our view of self-assessment as a constructive aid to individual learning instead of a potentially threatening evaluation device. Performance files are maintained on the Davis campus for all residents in the residency network program. This allows improved quality control for all of the educational programs, as well as improved counseling of residents.

The network self-assessment center provides an important approach to resident evaluation but is only one element of the required matrix which also includes the competency-based curriculum, audit of specific competencies and approaches for individualized learning based on needs as identified by periodic self-assessment. We are concerned with the continuous evaluation of knowledge, skills and attitudes of individual residents, as well as with evaluation of specific clinical rotations in each of the hospitals and model family practice units and the total evaluation of each affiliated program. Feedback from all teaching physicians and program directors is used regularly to evaluate individual resident performance. Videotapes are made of residents working with patients. These videotapes allow evaluation of interpersonal skills. The overall goal of our evaluation is to enhance each resident's learning, to improve each individual program and to assure that clinical competency objectives are being met.

Teacher Development Programs

A strong teacher development program for members of the clinical faculty is considered vital to effective resident teaching. Physicians may easily fall short of their potential as teachers because of lack of confidence, inadequate orientation to the program and to residents' capability levels, lack of understanding as to what is expected of them or of the residents, lack of familiarity with teaching techniques or other reasons. Periodic workshops are held on the Davis campus, as well as in outlying affiliated community hospitals, for all members of the network clinical faculty and deal with a number of subjects:

- Orientation to program objectives.
- Overview of residency program curriculum and residency capability levels in each residency year.
- Ingredients of effective learning experience.
- Roles of the teacher and the resident.
- Problem-oriented record as a teaching tool.
- Auditing of medical records.
- Teaching techniques with emphasis on critiquing approach.
- Use of self-instructional materials and self-assessment methods.

The teacher development program helps to increase the effectiveness of teaching by members of the clinical faculty in outlying communities, as well as increasing the satisfaction from resident teaching derived by participating physicians. Teaching and learning activities are seen as dynamic opportunities for continuing medical education for the participating physicians.

Resident Exchange

An essential principle of family practice resident training is that each resident's home base is the model family practice unit in his component program. There are, however, various opportunities for residents to acquire training elsewhere within the network program. As previously noted, residents in some programs, such as Merced, take their first year, together with medicine selectives in subsequent years, at Sacramento Medical Center. In addition, residents in any part of the University of California, Davis, Family Practice Residency Program may take electives in another part of the network based on their individual needs and the particular strengths of other parts of the program. For example, each affiliated program will have its own unique strengths, while some aspects of training will be best provided at the University base.

In addition to resident exchange within the network for electives, joint seminars are held periodically involving residents from each affiliated program. This provides an informal forum for interchange of ideas in areas of mutual interest and concern to residents in each affiliated program.

The preceptorship-locum tenens rotation is a required six-week rotation during the third resident year throughout the network. It is considered an important opportunity for an advanced resident to experience a real practice setting similar to that which he anticipates selecting on completion of his training. Every effort is made to allow the resident to select a setting which approximates as closely as possible the kind of setting he is anticipating for his own practice. Faculty within the Department of Family Practice then visit the practice, talk with the involved practicing family physician, survey the educational resources within the community and assure that adequate supervision will be provided for the resident—either within a group practice or in an association of other family physicians within a call system. It is required that the resident have consultation readily available for outpatients and for any patients admitted to hospital locally. The first two weeks of the six-week rotation are a preceptorship, during which the resident becomes acquainted with the practice, office staff, procedures and local medical community. The practicing family physician then returns to the University of California, Davis, for two to four weeks of postgraduate training which includes self-assessment through the network self-assessment center, individualized learning through the network teaching bank and individualized training using the resources of the Sacramento Medical Center. To date, six residents have completed this rotation and have uniformly considered it a highlight of their training program. They have been better able to select their electives during their third year after this experience and have been aided in their selection of a future practice setting. (Our first resident to take the preceptorship-locum tenens subsequently entered practice in the same community, an area of physician shortage.) The family physicians who have been involved in this exchange also have considered it a stimulating and useful opportunity for continuing medical education.

Comment

The development and operation of a regional network of affiliated programs is a collaborative effort involving the university and outlying communities. Teaching and clinical resources can be greatly expanded through an active partnership. By means of formal affiliations in family practice with outlying community hospitals, participating hospitals can realize a number of advantages:

- Assistance in residency program development through the pooled experience of other affiliated programs.
- Assistance with the establishment of educational objectives and evaluation of resident performance.
- Expansion of teaching resources through visiting professor programs and self-instructional materials.
- Augmented effectiveness of teaching through teacher development programs.
- Increased potential to recruit well-qualified program directors and teaching physicians.
- Enhanced potential for recruitment of residents of high caliber because of university affiliation and associated student clerkship programs.
- Increased opportunities for resident electives, both at the university and elsewhere in the regional network program.
- Certification of the resident's training by the university's Department of Family Practice.
- Access to allied health personnel being trained in other university programs, such as family nurse practitioners.

At the same time, the university will also realize a number of benefits:

- Increased opportunity to contribute to the training of an appropriate number of well-qualified family physicians.
- Extension of continuing medical education to a larger area beyond the medical school itself.
- Increased clinical resources for medical students, residents and allied health personnel.
- Opportunities to participate in the development of new models of education and health care delivery.
- Enhanced potential for research in family practice.
- Facilitation of improved linkages between primary, secondary and tertiary care.
- Augmented range of electives elsewhere in the network of affiliated hospitals for university-based family practice residents.

An excellent study of physician manpower needs in California was recently completed by the Comprehensive Health Planning Program of the State Department of Health. This study has addressed itself to an estimation of needs both in numbers and distribution of all clinical specialties throughout the state. General or family practice has been shown to represent the single most critical shortage field. The supply of family physicians will have to be increased by 44.8 percent in order to achieve an overall physician to population ratio of 1 to 2,000, which has been generally recommended as an "ideal" ratio.[10,11]

We are seeing a pronounced increase in interest by medical students in family practice. Many schools report at least 25 percent of their graduates are selecting careers in this field. The pressure is intense to develop an increasing number of family practice residency programs and positions, while still maintaining a high level of quality for these educational programs.

The regional network residency program is seen as a logical and effective approach in direct response to the pressing need not only to train more family physicians but also to encourage them to practice in areas where they are needed. This reorientation of medical education requires an effort involving university, community hospitals and practicing physicians. This approach can create closer and more productive interaction between the medical school and its region, and contribute to the quality of medical education and patient care.

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Refer to: Deisher JB: What is so special about a family physician?
West J Med 121:521-529, Dec 1974

Special Article

What Is So Special About a Family Physician?

JOSEPH B. DEISHER, MD, *Seattle*

Around a core of common, acute and chronic, recurrent health problems, a family physician must marshall the traditional episodic management for both inpatient and outpatient illness. He must also be especially adept at recently emerging routines of prevention and early detection. He provides individual and familial psychologic support and counselling, for both its therapeutic and preventive values. In addition, he must relate the individual care of his patient and the patient's family to the community as a whole. In doing this he will use not only his own skills but those of lay health volunteers, trained allied health care professionals and skilled subspecialists in the limited medical disciplines.

The proper preparation of family physicians for this complicated role has far-reaching implications for change in both medical education and medical practice.

THE CERTIFYING EXAMINATIONS of a specialty board should aim to test a candidate for his ability to perform the unique functions of that specialty. Residency training programs should provide training in those same functions. Now that the American Board of Family Practice (ABFP) has been established and accepted, the definition of family practice has an even greater practical importance than before. It is vital to define the functions of a specialist in family practice in order to assist in the planning of both the educational experience and the examinations. The first examinations of the ABFP were a "glorified Part III of the National Boards." There was little or nothing in them that should not have been answerable by a physician who has just completed a rotating internship. Is the 3-year residency in family practice meant to produce a glorified perpetual intern? Not likely.

One of the reasons why young physicians have tended so strongly to specialize in depth, rather than in breadth, has been the impossibility of becoming an expert in all specialties at a level of competence that warranted the respect of the top men in each specialty. Some physicians seem almost able to do this—but they are rare. It is futile for the family or general physician to attempt to compete in surgery with surgeons, in radiology with radiologists and so on. And yet,

The author is a member of the faculty of the Family Practice Residency program at The Doctors Hospital, Seattle, and Clinical Assistant Professor, Department of Family Medicine, University of Washington School of Medicine.

Reprint requests to: J. B. Deisher, MD, The Doctors Hospital, 909 University, Seattle, WA 98101.

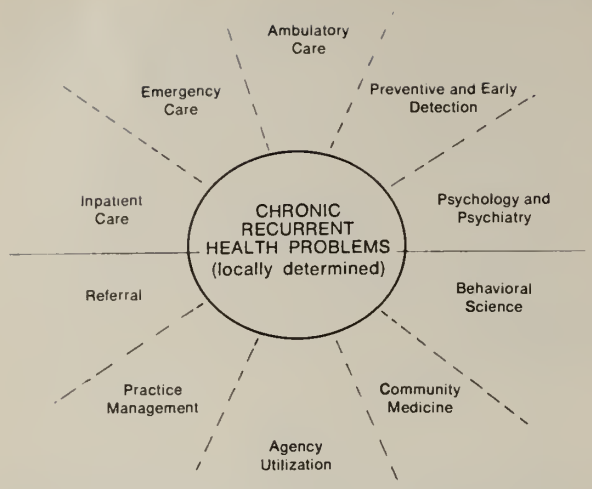

Figure 1.—Modern Family Practice. Major areas of knowledge and skill required of family physician.

no one wants to be thought a second-class doctor. In order that he may not fall into such a category, the special function of a family physician must be defined. This function is what departments of family practice must teach, and what the ABFP must examine for.

To define family practice using the traditional disease and treatment orientation is asking for second-class status when breadth of knowledge and the ability to organize family and individual health strategies are not highly valued. Such an approach leads to argument about what is and what is not a part of family practice. For example, is a dilation and curettement within the scope of family medicine—and what about first-time upper gastrointestinal bleeding? Simple cystoscopy? Reading an electrocardiogram? Reading an x-ray film of the chest? The list could go on and on.

The key to differentiating between a family physician and an old-style general practitioner lies in the assumption of a different responsibility by the family physician. The adjectives competent, continuing, comprehensive, conscientious and compassionate as applied to care have been insisted upon by the American Academy of Family Physicians since the beginning of its discussions in this field. To offer this sort of care (in place of the episodic, fragmented, one-man-24-hours-7-days-a-week type care traditionally provided by the stereotype general practitioner) requires that the new family physician have the knowledge and skills to develop a system of delivering health care which will necessarily involve many other personnel. He will be required to manage and direct a team of trained professionals, many of whom may have much more detailed knowledge than he in their specialized fields. They in turn will not have his breadth of knowledge and synthesizing skill.

Modern Family Practice

Defining the role of a specialty in health care is seldom a clear-cut matter. Mostly, it has to do with emphasis. Surgery is concerned with cutting, but there are many other essential aspects to surgery. Few argue over the relationship of these to the essential modality—the scalpel. Anesthesiology began with the relieving of pain during operations, developed an emphasis on the management of the unconscious patient and associated emergencies and, like other specialties, has a large but necessary foundation of basic medical and surgical information in support of these special functions.

There is a collection of definable skills which are specific aspects of family practice, not consignable to the catchall terms of general practice or "undifferentiated physician." Figure 1 shows the major areas of knowledge and skill required of a specialist in family practice. Of the ten segments, those above the horizontal line are largely traditional portions of medical training. They have generally, in the past, been taught with diminishing emphasis from left to right. Those below the horizontal line are the special areas of instruction in which emphasis must be added to professional education in order to produce a modern family physician.

The Focus of Family Practice

Wilson[2] identified the essence of family practice as an attitude. In truth, it is the sum of several attitudes. Together they represent an older philosophy of care which too often appears to have been lost in the busy episodic application of the miracles of modern medicine. This suggests that physicians may have forgotten the need to orient work, and therefore training, to the needs of the particular population that each physician is serving and to the local health problems they face.

For a family physician, the focus of his family practice (Figure 1) is a locally determined set of common health problems—acute, chronic or recurrent—which will be just a little different for each. The composition of medical practice and the kinds of knowledge and skills required may, in some instances, vary widely from one locale to another. Factors contributing to such differences include climate and the age, ethnic background,

local customs and degree of urbanization of the population. The training should be different for a family physician planning to practice in Homer, Alaska, than for one who will practice in Houma, Louisiana. One implication of this is that a family physician should be helped early in his training to formulate basic decisions about where he would like to practice. Will it be in an urban, suburban or rural area? In what sort of climate? Amid what sort of people? There is no denying that man proposes and God disposes, but with some general decisions of this sort, based on an analysis of himself and his intentions, he can begin to plot an appropriate course of study. As his studies progress, of course there will be a progressive sharpening of the details of that decision. Alternate goals and alternate studies will be selected which will help to meet expected functional needs more exactly.

One significant aspect of this philosophy is the patient-oriented commitment to design one's training and practice around the primary health needs of the patient community which selects one as their physician. This differs widely from the concept of restricting one's training and practice by arbitrarily selecting the health needs to be concerned with according to definitions based on anatomy, therapeutic mode, age, sex or causative agent—and accepting only those patients who fit the criteria.

The family physician must be committed also to dealing with those common illnesses of man for which there is no cure, only control—and often little of that. These diseases are mostly chronic, usually non-lethal, often progressively crippling. They are frustrating to treat because of the difficulty of resolution. Often their control depends upon the arduous process of remolding the patient's life-style, or even his personality. To be content in family practice, the physician must make an informed choice based on a thorough knowledge of himself. He must decide whether the health of his patients (promoted through low-key, persistent efforts at prevention, early detection and early treatment of common illness) will provide the professional satisfaction he requires, or whether he must have frequent infusions of the drama and anxiety and proud gratification which can come from the episodic saving of life or limb.

To many it is not enough to recommend the use of seat belts and safe-driving practices rather than deal proficiently with the injuries resulting from the traffic accident. It is more taxing to the therapist to modify the patterns of interaction within a family than to prescribe diet and antacids—and occasionally surgical procedures—for the ulcer induced by existing patterns. Satisfaction with this sort of commitment to the humbler approach requires a high level of insight, maturity and self-knowledge. A commitment to treating the chronic and recurrent common diseases implies a continuing of responsibility to the patient and the patient's problems, competence in medical knowledge, skill in human relations, and the compassion to avoid with dignity the too-frequent trap of the educated man—arrogance or hauteur.

Ambulatory Care

The topmost of the peripheral segments of Figure 1 indicates that health care by family physicians is provided predominantly to ambulatory patients. Kerr White[1] has shown that a small minority of people who have health needs are admitted to a hospital. A family physician is, to most of his patients, *the* point of access to the health care system. He is the primary physician who deals with the "vertical" patient over a horizontally broad spectrum of health activities, as opposed to the limited specialist who deals with the "horizontal" (bed) patient in a very deep and intensive manner. Skill in providing ambulatory care, then, is a major need for a family physician and his coworkers. Primary care includes two segments which may be called health care and healing care. The first comprises those activities of health and medical personnel especially related to preventive maintenance. The second aspect, healing care, applies to activities directed to those who are not well. Definitive, early diagnosis may well require astute observation, often over a period of several visits, in addition to sound medical judgment. The implication of this concept of two related kinds of care for teamwork among health professionals has great bearing on the training program in family practice.

Emergency Care

Access to care includes emergency access and ordinary, planned access for non-emergency reasons. For practical purposes we must concede that an emergency exists whenever the patient needs, or feels that he needs, immediate attention to a health-related problem. The key word is immediate. Time is of the essence in any definition of emergency. Many "emergency" patients can be

treated simply and sent home. This is particularly true when the treatment is provided by a tenured family physician who is familiar with the patient and his family. Because a fairly large percentage of emergency patients will need to be admitted to the hospital as inpatients for observation or more definitive care, a family physician must be capable of perceptive triage as well as appropriate definitive treatment in the emergency room. He must also have the privilege to admit his patients under his own care, as well as to call for consultation or referral. A family physician needs to learn enough about emergency care to manage the less complex medical emergencies of his patients and to identify the larger ones. For the latter, he must be able to provide adequate first aid preparation for transportation including cardio-pulmonary resuscitation and the management of fluid and electrolyte balance. He must be knowledgeable in arranging for care by a limited specialist in those cases where he deems it necessary, and always he must provide his personal support to the patient and to the family.

Inpatient Care

A family physician should be adept at providing inpatient care for common conditions requiring admission to hospital. He must be afforded hospital staff privileges commensurate with his training and based on personal evaluation of skills by the local staff of the hospital where he takes his patients. There is a large group of common (though serious) illnesses, including some whose best therapy is surgical, which a family physician should be capable of managing as well as and often better than the limited specialist. To many of the latter, the commonplace sometimes seems to have become so mundane as to receive less than the fullest and finest attention. The process of referral should be a well-developed skill of a family physician and he should have a well-established network of resource physicians to whom he refers his families with every confidence of good care and consistent, thoughtful "dereferral." Although the primary physician deals most often with the "vertical" patient, who is entering the health care system for a brief time, he also functions importantly in returning the patient who has been in a hospital for a longer period to (as nearly as possible) his functional vertical position in his family and community. Through active participation in inpatent care, he facilitates his management of this rehabilitation process.

Health Maintenance

The three aspects of family practice listed so far have been the only segments of family practice taught with any great emphasis in most medical schools and residency programs until recently. Disease prevention and early detection have usually received brief didactic coverage in courses on epidemiology and public health, and have proved less than exciting for most students. In contrast, methods of prevention and early detection of disease not only have become broadly feasible in modern health; they also offer the major hope for decreasing the devastating costs of medical care and hospital stays. Many of the details of prevention and early detection, since they constitute health care rather than healing care, can be performed by middle level practitioners. However, the planning and the overall reporting to the patient of the outcome of activities related to health maintenance and prevention will often require the authority of the physician.

Until recently, the technology of health maintenance has been very sparse. However, there is a growing body of knowledge concerning the early detection of a number of common illnesses which often have significant impact on a patient's life and about which something can be done if they are detected in the early stages. Information is accumulating on the correlates of subsequent illness to the extent that health hazard appraisal is now a recognized technique for encouraging patients to change life-styles and habits known to be likely to lead to ill health in the future. Screening programs have proven able to uncover more handicaps than the health care system can handle comfortably. This technology must be made part of the armamentarium of the primary physician.

Health maintenance also includes the management of minor, though annoying physical adaptive changes which are simply overactive physiological variations within the patient. In the course of skillful minor care, the detections of recurrent patterns of these minor problems may lead the astute, well-trained observer to detect a major, underlying, insidious common cause while it is still in an early and treatable phase. For example, repeated asthma in a child or young adult leads eventually to permanent lung damage and disability. Repeated bouts of peptic ulcer may produce serious complications such as obstruction, perforation or hemorrhage. Repeated bouts of temporary blood pressure elevation associated with episodes of fear or anxiety seem to be a part of the natural history

of the development of irreversible hypertension. If, through skillful management not only of the episodes but of the life-style and family setting of the patient, these antecedent episodes can be minimized, their deleterious consequences will be minimized also. Early recognition and skillful management of chronic urinary tract infections in girls has the same potential for promoting health. This sort of health maintenance activity holds perhaps the most practical promise of the whole concept of continuing care and the maintenance of continuous family records.

Psychology and Psychiatry

In the field of prevention also lie many matters of psychological evaluation and supportive psychiatry for the individual patient and for the family. Carmichael[3] estimates that a family physician, after a period lasting up to two years, acquires tenure in the family constellation of most of his patients. From this position of security and trust, he can provide insights and supportive strength in a unique way. Major intervention in the province of the psyche, however, should be dependent on demonstrated skill, just as in the more physical domains of medicine.

Out of the training for family practice must come for each student a philosophy of the nature of man and his needs. A general concept of the mechanisms of motivation is an essential part of such understanding. Equally important are recognitions of the validity of personal idiosyncrasy and the life style determination. A new family physician should be acquainted with various normal and pathological states of consciousness including sleep and its disturbances, alcohol and drug use, transference, hypnosis and meditation. He must be able to understand the ubiquity of depression and its role in the production of disease. Along with this goes an understanding of the common need for dreams and minor delusions. The non-judgmental approach, which leads to compassionate care as well as detached concern, is even more important for a family physician than for the limited specialist.

A fair degree of self-knowledge is an essential prerequisite to effective patient and family management in family practice. To help student-physicians understand the psychopathology of their own everyday life should be one of the instructional objectives of training in family practice.

Behavioral Sciences

The traditional individual psychologic and psychiatric concerns merge almost imperceptibly with the management of family problems through understanding of the social sciences. Practical ways of using the fund of social scientific knowledge have only recently been subjected to study and disciplined organization for therapeutic use. This new understanding includes a knowledge of the operation of small groups and the normal growth and development of both individuals and family units. The modern concept of the family encompasses any group of people living together more or less permanently, whether or not they have blood or legal ties. Prevention and early detection of destructive interaction in the family, and the treatment of established interpersonal problems are part of the specialty of family practice. Milieu, group and family therapy are all useful tools about which knowledge and skills must be acquired. Knowing when to refer patients and families to a social worker, psychiatrist, clergyman, lawyer or therapeutic group, and how to manage the transferral of care must be part of the training for family practice. The weaving of this sort of knowledge into the specific treatment plan for individual health and medical problems is a skill to be learned. The accommodation of treatment strategy to the various cultural patterns determines the efficiency of such treatment in terms of patient compliance with plans.

The art and science of communication is perhaps best mentioned here. Defective communication, both in sending and receiving, is perhaps the most widespread and insidious cause of problems for the individual physician, his patients and medicine as a profession today. Interviewing is a basic technique which is very important to family physicians. Here active listening is an essential in which many physicians are quite untutored but which is fundamental to effective family practice. The communicative aspects of interaction and transaction are equally basic to family and primary care.

It has become more and more obvious that there is a need for the physician and other members of the health team to be teachers. Doctor, in fact, means teacher. The goal of education is planned change of behavior. This is exactly what health maintenance is all about. An elementary knowledge of educational processes will not only allow the physician and other members of the

health team to teach patients; it will assist them in their own continuing education efforts so that they may maintain a high degree of competence throughout their careers.

Community Medicine

Once the medical perspective has enlarged from the individual to his family, the physician is already dealing in the area of group health. To deal with community medicine, he needs only to enlarge his area of concern to include the block, the neighborhood and the larger community. Community medicine is the practice of medicine with the community as the patient, and it requires the same elements of ethical responsibility, rationality and patient involvement and compliance as does the practice of any other kind of medicine. Consideration of the organ, the individual and the community as a series of interacting systems provides a universally applicable perspective for the health professional, the major variable being the degree of magnification. The patient's disease (or well-being) is so intimately related to his setting that the holistic view of one person necessitates a workable comprehension of the community. There are basic patterns of community operations, entry, politics and group influence that should be as much a part of the armamentarium of a family physician as his knowledge of cellular processes.

Understanding of the cultural patterns of his patients and their impact on what has been traditionally called public health must be an automatic consideration by a family physician in his diagnosis and planning for treatment. The relationship of civic economies, the concept of the "community of solution," and an understanding of the social foundations of professional care are essentials in the curriculum of a family physician. These and other aspects of community anatomy and physiology must form, with the traditional aspects of health career training, a matrix of consideration and understanding. The pilot examples of this sort of community action are slowly taking shape relative to the development of fully integrated and coordinated emergency medical services throughout an area, and in reference to certain environmental protection programs.

Use of Agencies

A full working knowledge of the operations and assistance offered by agencies within the community which relate to various aspects of health and helping is an important aspect of a family physician's ability to assist his patient. One of the greatest gaps in our health system today is between the patient and the very numerous agencies available to help him. These may be governmental or private, for profit or not for profit, medical or social, voluntary or professional. Unfortunately, they are most often unknown to those who need their help the most. Referral to such agencies of a quasi-medical nature should be done as skillfully and thoughtfully as a purely medical referral.

This aspect of health care management will doubtless be emphasized most in the latter phases of family medicine training but awareness from the earliest days of the interrelationship of physician and these other members of the health team is an important instructional objective. Increasing experience with such team-members-in-training seems advisable during a family physician's training years.

Practice Management

Bringing together a patient and his community resources relates closely to the whole area of practice management, operating an office and establishing relationships between the doctor's personal practicing conditions and the other health institutions and professionals. The manner of practice management determines and is determined by the patterns of referral from the family physician's office to other agencies, institutions and individual practitioners. The use of middle-level practitioners and other allied health personnel will become more common at an exponential rate as national health insurance in one form or another is enacted. The management of the team and the skillful use of each member's talents for the greatest benefit of the patient will be new and exciting challenges to the leadership ability of family physicians. The team can be expected to include administrators and other non-clinical consultants for most family practices in the near future. The spectrum of arrangements for health care delivery from solo practice to the multi-branched group, will be a vital portion of the knowledge of the family and community physician, and constitute a legitimate and badly needed area of research for academic departments of family medicine. Here again, heavy emphasis is more acceptable late in the training period but the awareness of potential need is important throughout the family medicine curriculum.

Specific training areas in the field of practice

management include the elementary principles of personnel management, financial management, simple bookkeeping, business law, business insurance and customer relations. While not taking a great deal of time for each subject area, training in family practice should supply adequate general references for future use, and a fundamental vocabulary which will permit the physician to learn, with a little practice, to skillfully guide his own affairs, as well as those of his patients. Somewhat more detail could be included about health insurance, both governmental and private, and some concepts of welfare provisions of a general nature.

Referral

For some of the major problems of care related to specific episodes, especially in the "horizontal" patient requiring admission to the hospital, a family physician will need to obtain consultation or refer the patient to a limited specialist. He should learn to do this skillfully and easily, with assurance from his colleague that the patient will be returned to him for continuing family care as soon as the critical episode has been dealt with.

Correspondence between members of the health team in referring patients for consultation and in "dereferring" patients from the consultant back to the patient's principal source of care constitute a subject which requires considerable thought and sensitivity. Abstracting the significant parts of a clinical problem in a referral note, rather than a total recall description, is a knack that more physicians should acquire.

The subject of referral has been little examined in a formal way. There are many inherent difficulties which make for friction and poor communication between members of health care teams and patients, and within the team itself. The subject called medical ethics has dealt imprecisely and inadequately with these problems in the past. The ability to listen well, and the strength to make overall managerial judgments, even those which may contravene one or another consultant, are virtues a family physician can only acquire through study and practice.

Educational Implications

Sound educational principles demand that training for a family physician be based on a clear definition of the tasks—the role—that he will assume in practice. In sum, he will be expected to design a system of delivery of health care that is custom-tailored to the needs of each of his patients. He will personally perform some of the necessary functions for entry into and exit from the system among his duties as a primary care expert. More important, perhaps, will be his ability to organize separate segments of the health care delivery resources of the community in which he chooses to practice so that they will best serve the individual needs of his patients. In the years ahead, when those presently in training will be putting that training to the test, there will be more and more emphasis on prevention—primary, secondary and tertiary. Almost equal emphasis will develop related to cost control, not only of the immediate episode of care but in reference to health planning. Family practice training today must include a liberal portion of community medicine, as well as economics and management processes.

In order to fashion the necessary personal health care plans required by his patients, a family physician will need to be fully up-to-date on medical and surgical technology and its potential, but the more esoteric details will only rarely be essential to such planning. Today's training, then, must curb the tendency of most limited specialties in faculty positions to teach ever more deeply into their subjects, and must promote the development of connecting insights which link one intensive discipline with another. The interlocking of such linkages is the special technologic subject matter of family medicine.

To perform adequately the tasks listed here will require an artistic level of skill in the sensitive management of communications between two people, among groups of people and among the several facets of the individual patient's own personality. The specialist in family medicine can no longer afford to pass so much of the burden of this sort of activity over to the nursing profession. Training—guided, reflective training—in communication processes must be a major part of the instruction in the undergraduate and graduate programs in family practice.

It seems clear that the concept of *synthesis* is the key to the mode of operation of the family physician of the future. Wilson[4] speaks of the synthesizing function of this "new specialist." This synthesizing function is one of assisting the patient in the coordinating and integrating of his personal health needs with his other needs and aspirations within the setting of his family and community. It

is the family physician who works out the overall health strategy. It is he who interdigitates the activities of the health team, as a conductor coordinates members of an orchestra. It is he who assures that both the patient and those around him understand their health and medical situation and what can be done to improve it. For instance, if a diabetic who must carefully curb his caloric intake is married to a woman whose major successes in life derive from cooking delicious, high-calorie food for those she loves, their family physician must assist them to manage the adjustment of lifestyle required to accommodate both the patient's health and his marital situation. There have been physicians who have done this under the traditional system based on traditional education, but they have been unusual. The growth of interest in and need for family physicians requires that those responsible for the medical education system design curricula to teach this sort of skill. This is the synthesis of a health related program-of-living incorporating detailed medical knowledge, intimate psychologic understanding and interactional management skills. The number of variable yet manageable factors in this sort of operation equals or exceeds those involved in the most complex medical and surgical procedures within the anatomy of one individual or a single organ.

The use of the word "synthesis" here is significant from another perspective. In educational circles, to attempt the evaluation of the ability to synthesize from one's knowledge and understanding is to work at the most difficult level of testing.[5] Synthesis is impossible to parrot—to learn by rote. It requires participation, personal expression, ingenuity and high levels of knowledge and commitment. It has been noted that testing for the art of medicine is rarely included in professional examination. Perhaps the intuition of the teacher has been that those who were ready to learn it, would assuredly pick it up; that those who were not ready, could not pick it up; that even if it were taught there was no way to articulate the content anyway, and that he could evaluate it through acquaintance and contact with the student. This will not suffice for the teaching of family medicine. We must believe that we can describe what we think. If we can recognize good family medical practice, we must dredge up the words to articulate what it is we mean by such an expression. We are obliged further to articulate these concepts so they are intelligible to others—intelligible enough so that consensus on both curricular objectives and evaluation can be achieved. As always in the process of evaluation for certification purposes, the concern here is for setting of minimums—for building a floor of assurance—relative to necessary knowledge and, we hope, to consequent performance.

The challenge to educators in family practice, then, is to train a professional who can synthesize the various factors of each patient's predicament into a continuing life-style with the highest level of potential for promoting health, and to devise ways to test his ability to do so. This is an unusual assignment. Most current educational programs heavily emphasize activities in which the student functions as consumer-and-critic of ideas, rather than producer-and-synthesizer. Synthesizing requires the organization of ideas, often in new and novel ways, always in ways tailored to a special situation, and sometimes the development of ideas that are totally original.

Perhaps the most important implications are that this is communication, that communication requires synthesis and that this whole process is art. The effective communication of even a relatively common idea to a specific person for whom it happens to be new is, in its way, a work of art. The development and conveying of a program of health care to a patient and his family in such a way as to achieve compliance (and consequent beneficial results) must be accorded the status of artistry in many cases—the art of medicine. Leonardo de Vinci described perfection in art as that construction from which nothing could be taken away and to which nothing could be added without diminishing its impact. This is a definition of elegance. It is also a definition of good medicine—especially good family medicine.

Summary

Although fulfilling needs as old as mankind, although based on a long and honorable tradition, the role of family physician and the education for it cannot, of necessity, follow the traditional pattern. Instead, it must be aimed, through use of the most up-to-date information available, toward a new sort of practice set in the future. Restriction by traditional mold would set the stage for another failure in the efforts to provide the levels of care which are often achievable but not so often available. To a degree depending only on his interest and ability, the family physician of the future will become a manager of health and health care systems; a solver of complex health problems for

the family and community and an advisor, confidant, friend and advocate after the manner assumed by many astute physicians of the past but seldom specifically prepared for in their training. The provision of a constantly available resource in time of emergency, a guide to the complexities of the health care system and an advisor on a vast array of complicated decisions of life are functions which have always been a part of family practice. In the past, however, there has been little directed training for these. Underlying these and all the other functions of a family physician must be a profound intuitive and instructed understanding of human life and its interrelations. In the past this material has seemed too complex or too simple or too intimate to be taught. We have now progressed to a stage where these things can be brought into consciousness and identified as learning objectives.

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Length of Medicare Hospital Stays by Region

MEDICARE PATIENTS in the West had significantly shorter hospital stays in 1970 than those in the Northeast for treatment of the same medical conditions, a Social Security Administration study has found.

The report, titled *"Medicare 1970: Length of Stay by Diagnosis,"* was issued by Social Security's Office of Research and Statistics. It found differences in hospital stays of up to 50 percent between the two regions.

The average length of stay nationally was shown at 12.8 days. In the Western states, the average stay was 10.1 days; in the South, 11 days; in the North Central states, 13.1 days; and in the Northeast, 15 days.

The study was based on a sample of 5.5 million discharges of Medicare patients from short-stay hospitals in 1970. The differences in length of stay between regions carried through all age groups over 65 and in cases with surgery, as well as those without surgery.

Women diagnosed in the West as having breast cancer had an average hospital stay of 11.1 days. In Northeastern hospitals, the average stay for treatment of breast cancer was 16.4 days.

Other examples of the differences in hospital stays between the two regions were:

- Arteriosclerotic heart disease: West, 9.7 days; Northeast, 15 days.
- Acute coronary occlusion: West, 13.9 days; Northeast, 18.3 days.
- Fractured femur with two or more diagnoses: West, 22 days; Northeast 29.5 days.
- Malignant neoplasms of the cervix: West, 7.5 days; Northeast, 16.5 days.

There were no major differences in length of hospital stays between the Southern and North Central states, the report showed. For example, treatment of breast cancer produced an average stay of 14.5 days in the South and 15.7 days in the North Central states. Treatment for arteriosclerotic heart disease required 11.5 days of care in the South and 13.3 days in the North Central states.

Single copies of *Medicare 1970: Length of Stay by Diagnosis* [DHEW Publication No. (SSA) 74-11704] may be obtained free from the Publications Staff, Office of Research and Statistics, Social Security Administration, 1875 Connecticut Avenue, N.W., Washington D.C. 20009. The report may be obtained in quantities through the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. (Stock No. 1770-00236) at $2.40 a copy.

CONSULTANTS FOR

The Western Journal of Medicine in 1974

The editors wish to acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given by the following persons to The Journal during the past year.

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Dallman, Peter R.
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deLorimier, Alfred A.
Diamond, Louis K.
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Drutz, David J.
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Dunphy, J. Engelbert

Eastman, Henry V.
Eisenberg, Eugene
Engleman, Ephraim
Epstein, John H.
Epstein, Wallace

Fasal, Paul
Felt, John
Fenlon, Roberta
Filler, Morey
Finch, Clement A.
Fishman, Noel H.
Fox, E. R.
Frick, Oscar

Gallagher, Donald M.
Gershengorn, Kent
Gertz, Edward
Gitnick, Gary L.
Glynn, Kevin P.
Gold, Warren M.
Goldman, Leon
Goldman, Robert H.
Goldsmith, Robert
Gordan, Gilbert S.
Gordon, Jack D.
Gotch, Frank A.
Grausz, Henry
Greenberg, Robert E.
Greenspan, Francis
Greer, Monte A.
Griffeath, Harold I.
Grossman, Moses
Grumbach, Melvin M.
Gulyassy, Paul
Guze, Lucien B.

Hamilton, William K.
Harrison, Donald C.
Hassard, Howard
Heyneman, Donald
Hine, Charles H.
Hinman, Frank, Jr.
Hoeprich, Paul
Hollenberg, Milton
Holliday, Malcolm A.
Hollister, Leo
Hopewell, Philip

Indianer, Leo
Inman, Verne T.

Jacobs, Edwin M.
Jawetz, Ernest
Johanson, Craig
Juul, Clement O.

Kadin, Marshall
Kan, Yuet
Kaplan, George W.

Karam, John
Katz, Ronald L.
Kempson, Richard L.
Klutch, Murray
Koler, Robert D.
Krikes, Nicholas P.
Kriss, Joseph P.

Layne, John A.
Layzer, Robert B.
Lee, John
Lee, Philip R.
Leeds, Paul H.
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Margolis, Alan J.
Markham, Charles H.
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Masouredis, Sam
McCormack, Kenneth R.
Meyer, Karl F.*
Millar, Max S.
Morrelli, Howard F.
Moser, Kenneth
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Nadel, Jay A.
New, Paul F. J.
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Pappagianis, Demosthenes
Parmley, William W.
Perloff, Dorothee L.
Pevehouse, Byron C.
Phillips, Theodore L.
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Ramer, Barry S. M.
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Shearn, Martin A.
Sheldon, George F.
Sheline, Glenn E.
Shohet, Stephen B.
Shore, Richard S.
Silverman, Sol
Slager, Ursula T.
Spivack, Samuel D.
Smith, David E.
Smith, Donald R.
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in memoriam

Crawford, Donald J., Long Beach. Died October 1, 1974 in Long Beach of heart disease, aged 61. Graduate of University of Southern California School of Medicine, Los Angeles, 1940. Licensed in California in 1940. Dr. Crawford was a member of the Los Angeles County Medical Association.

Day, Harold Ellsworth, Dana Point. Died June 14, 1974, aged 56. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1944. Licensed in California in 1949. Dr. Day was a member of the Orange County Medical Association.

Dubin, Hyman Mayer, Alhambra. Died October 2, 1974 in Los Angeles of atherosclerosis, aged 68. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938. M.D. degree from California College of Medicine, 1962. Dr. Dubin was a member of the Los Angeles County Medical Association.

Ferrand, Paula Thon, San Francisco. Died October 14, 1974 in San Francisco, aged 74. Graduate of Uniwersytet Jana Kazimierza Wydzial Lekarski, Lwow (Lemberg), 1925. Licensed in California in 1963. Dr. Ferrand was a member of the San Francisco Medical Society.

Greene, Charles Henry, San Francisco. Died September 28, 1974 in San Francisco of heart disease, aged 74. Graduate of Albany Medical College, 1932. Licensed in California in 1950. Dr. Greene was a member of the San Francisco Medical Society.

Hall, James Hinquong, San Francisco. Died October 6, 1974 in San Mateo, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1922. Licensed in California in 1922. Dr. Hall was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Herschel, Paul E., Richmond. Died October 17, 1974 in Richmond of brain cancer, aged 51. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1951. Licensed in California in 1951. Dr. Herschel was a member of the Alameda-Contra Costa County Medical Association.

Kading, Earl C., Sharp Park. Died in September 1974 in Saratoga, aged 80. Graduate of Rush Medical College, Chicago, 1919. Licensed in California in 1924. Dr. Kading was a retired member of the San Mateo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Love, Jesshill, Santa Barbara. Died October 1, 1974 in Santa Barbara of heart disease, aged 68. Graduate of the University of Louisville School of Medicine, 1929. Licensed in California in 1960. Dr. Love was a retired member of the Santa Barbara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Lovin, Bailey J., jr., Reseda. Died September 26, 1974 in Reseda of heart disease, aged 53. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1951. Licensed in California in 1951. Dr. Lovin was a member of the Los Angeles County Medical Association.

Miller, Clark R., Glendale. Died September 27, 1974 in Glendale of myocardial infarction, aged 60. Graduate of George Washington University School of Medicine, Washington, D.C., 1940. Licensed in California in 1946. Dr. Miller was a member of the Los Angeles County Medical Association.

Novy, Frederick G., jr., Berkeley. Died October 7, 1974 in Oakland of massive gastrointestinal hemorrhage, aged 72. Graduate of University of Michigan Medical School, Ann Arbor, 1927. Licensed in California in 1933. Dr. Novy was a retired member of the Alameda-Contra Costa County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Pandes, Jose Verdeflor, Daly City. Died October 15, 1974 in Daly City of heart disease, aged 51. Graduate of Faculty of Medicine and Surgery University of Santo Tomas, Manila, 1954. Licensed in California in 1969. Dr. Pandes was a member of the San Francisco Medical Society.

Petty, William, Santa Maria. Died October 2, 1974 in Santa Maria, aged 65. Graduate of University of Pittsburgh School of Medicine, Pittsburgh, 1933. Licensed in California in 1944. Dr. Petty was a retired member of the Santa Barbara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

SCANLON, WILKO GRUVER, Pasadena. Died September 20, 1974, aged 77. Graduate of Vanderbilt University School of Medicine, Nashville, 1923. Licensed in California in 1927. Dr. Scanlon was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

SHIRLEY, HALE FOREMAN, Palo Alto. Died October 7, 1974 in Palo Alto, aged 73. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1956. Licensed in California in 1957. Dr. Shirley was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

SPENCER, JAMES EDGAR, Walnut Creek. Died September 20, 1974 in San Francisco of myasthenia gravis, aged 63. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1936. Licensed in California in 1936. M.D. degree from California College of Medicine, 1962. Dr. Spencer was a retired member of the San Luis Obispo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

STEINBECK, FELICE, Thousand Oaks. Died in October 1974 in Thousand Oaks, aged 63. Graduate of Medizinische Fakultät der Universität, Wien, 1935. Licensed in California in 1942. Dr. Steinbeck was a member of the Los Angeles County Medical Association.

TAFT, JOHN HARRIS, Paradise. Died September 28, 1974 in Paradise, aged 62. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1935. Licensed in California in 1935. M.D. degree from California College of Medicine, 1962. Dr. Taft was a member of the Butte-Glenn Medical Society.

WARNOCK, ERNEST HENRY, San Marino. Died October 1, 1974 in San Marino of leukemia, aged 71. Graduate of Indiana University School of Medicine, Bloomington, 1932. Licensed in California in 1939. Dr. Warnock was a member of the Los Angeles County Medical Association.

AUTHOR INDEX

Abbott, Joseph A., San Francisco 473
Ackerman, William J., San Diego 428
Alpers, David H., St. Louis 499
Amacher, Peter, Santa Ynez, CA 350
Armentrout, S. A., Irvine 1
Atkinson, J. Hamp, La Jolla 112

Bachrach, Reinhard J., Salinas, CA 508
Ballinger, Walter, San Francisco 329
Barber, Joan, San Jose 430
Barbour, Benjamin H., Los Angeles 439
Barkan, Howard, San Francisco 150
Bartlett, John G., Sepulveda 390
Beals, Rodney K., Portland 321
Behrstock, Barry B., San Francisco 140
Benner, E. Jack, Sacramento 173
Benson, John A., Jr., Portland 462
Berci, George, Los Angeles 6
Bergin, Dan, Sacramento 106
Berkowitz, S., Burlingame 151
Blaisdell, F. William,
San Francisco 71, 153, 240, 329, 435, 510
Brewin, Austin, San Francisco 232
Brewster, F. Michael, Concord 142
Bristow, Lonnie R., San Pablo, CA 77
Brotman, Martin, San Francisco 504
Brown, Thomas C., Davis 514

Carey, Joseph S., Los Angeles 274
Carey, William D., Rochester, Minnesota 504
Chan, Richard, Sacramento 173
Chan, Tsoi T., Portland 462
Chesbro, Wayne P., Berkeley 328
Chin, James, Berkeley 94
Clark, Kemp, Dallas 229
Clarke, James S., Sepulveda 390
Cleveland, Kitty, La Jolla 112
Coburn, Jack W., Los Angeles 22, 508
Cohen, Peter, San Francisco 300
Cohen, Sheldon E., Davis 449
Connett, Mahlon C., Concord, CA 324
Conyers, Cary L., Santa Barbara 270
Cullen, P. Kent, Jr., Santa Barbara 270

Deisher, Joseph B., Seattle 521
DeLuca, H. F., Madison, Wisconsin 64
Diamond, Shirley G., Los Angeles 188

Emmons, Richard W., Berkeley 142
Engels, Judith L., Sacramento 179
Epstein, Ervin, Oakland 236

Fair, William R., Stanford 366, 374, 382
Feldman, Martin I., Davis 449
Filly, Roy A., Stanford 362, 374, 382
Finegold, Sydney M., Los Angeles 390
Fisher, Stan R., Irvine 439
Floch, Martin H., Norwalk, Conn. 423
Franco, Jorge A., San Jose 328
Friedland, Gerald W., Stanford 362, 374, 382
Frykman, Gary K., Loma Linda 265

Gassaway, Alexander R., Portland 254
Gay, George R., San Francisco 106
Geyman, John P., Davis 514
Geis, Gilbert, Irvine 161
Gershman, Martin M., San Francisco 69
Gittes, Ruben F., San Diego 91
Goodley, Paul H., Davis 239
Goodman, Stanley J., Torrance, CA 207
Goodner, Ernest K., San Francisco 291
Goodwin, Willard E., Los Angeles 328
Gorbach, Sherwood L., Sepulveda 390
Govan, Duncan E., Stanford 362, 374, 382
Green, Joseph P., San Diego 91
Greenspan, Francis S., San Francisco 359
Greer, Monte A., Portland 425
Guillozet, Noel, King City 249
Gullion, David S., San Francisco 123

Hartenbower, David L., Los Angeles 22, 508
Hattersley, Paul G., Sacramento 179
Heiner, Douglas C., Los Angeles 152
Hirschfeld, David S., San Francisco 473
Hoff, Julian, San Francisco 435
Hoffer, Paul B., Chicago 137
Hurwitz, Samuel, San Francisco 443
Hurwitz, Sheldon R., San Diego 91

Inaba, Darryl S., San Francisco 106

James, Thomas N., Birmingham, Alabama 496
Jamison, Rex L., Stanford 434
Johnson, Ernest W., Columbus, Ohio 237
Johnson, William W., Los Gatos 433

Katon, Ronald M., Portland 462
Kay, Jerome Harold, Los Angeles 70
Keeffe, Emmet B., Portland 462
Keller, Margaret, La Jolla 45
Kempe, C. Henry, Denver 229
Kennedy, J. H., Portland 152
Kern, William H., Los Angeles 185
Kessler, Warren O., San Diego 91
Kohlman, Richard J., San Jose 244
Krick, James A., Stanford 235
Kunin, Calvin A., Madison, Wis. 421
Kunkel, Fred, San Francisco 473

LaJoie, William J., Palos Verdes 238
Lambert, Mark C., San Francisco 439
Lennette, Edwin H., Berkeley 94
Levine, Rachmiel, Duarte, CA 426
Levine, Victor D., Los Angeles 501
Long, Howard F., Pleasanton 235

Magoffin, Robert L., Berkeley 94
Markham, Charles H., Los Angeles 188
McMillan, Donald E., Santa Barbara 350
Melnyk, Clifford S., Portland 462
Mendoza, Stanley A., La Jolla 45
Menzer, Lawrence L., Northridge, CA 147
Meyers, Marvin H., Los Angeles 100
Munzinger, Jurg P., Sacramento 173

Nelson, Bernard C., Berkeley 142
Nemiroff, Robert, San Diego 112

Newmeyer, John A., San Francisco 106
Noe, Joel M., Stanford 430
Norman, Anthony W., Riverside 22, 508

Overturf, Gary D., Los Angeles 501

Palmer, Philip E. S., Davis 10
Panish, Joel F., Los Angeles 6
Parnell, Francis W., San Rafael 349
Perkins, Woodbury, San Diego 342
Peters, Robert, San Francisco 473
Petrakis, Nicholas L., San Francisco 140
Pevehouse, Byron C., San Francisco 298
Plested, William G., Los Angeles 274
Prince, Barbara, San Francisco 297

Rector, Floyd C., Jr., San Francisco 302
Remington, Jack S., Stanford 235
Rhame, Frank S., Stanford 66
Robbins, Alvin, La Jolla 112
Rom, William N., Sacramento 10
Roney, James G., Jr., Los Altos 83

Sacks, Stephan A., Los Angeles 433
Scheinman, Melvin M., San Francisco 473
Schmerl, E. Fritz, San Leandro 151
Schrier, Robert W., Denver 62
Schwarz, M. Roy, Seattle 333
Scott, Calvin, Los Angeles 274
Shapiro, Marvin J., Encino, CA 328
Siperstein, Marvin D., San Francisco 404
Smith, John L., La Jolla 144
Sokoloff, Burton, Canoga Park, CA 509
Specht, Elmer E., San Francisco 150, 281
Starr, Albert, Portland 319
Steele, Muriel, San Francisco 240
St. Geme, Joseph W., Jr., Torrance 456
Stoner, John R., San Francisco 482
Stunkard, Albert J., Stanford 138
Sullivan, Peter, Bethesda, Maryland 232
Swanson, Phillip D., Seattle 228
Szalay, Glenn C., Harbor City, CA 328

Takahashi, Masato, Los Angeles 147
Tanagho, Emil A., San Francisco 292
Tedesco, Francis J., St. Louis 499
Thomas, Arthur N., San Francisco 510
Treciokas, Leo J., Los Angeles 188
Trunkey, Donald D.,
San Francisco 71, 153, 240, 329, 435, 510

Ulrich, R. F., Cleveland 1
Usselman, James A., La Jolla 144

Wagman, Allan J., Los Angeles 185
Wasson, Eugene C., III, San Diego 144
Watts, H. David, San Francisco 50
Weinberger, Caspar W., Washington, DC 158
Werner, S. Benson, Berkeley 66
Whitehead, Craig A., San Francisco 106
Wilson, Samuel E., Los Angeles 390
Wolfman, Earl F., Jr. 449
Wood, Virchel E., Loma Linda 265
Wylie, Edwin J., San Francisco 71

Yoshikawa, Thomas T., Torrance, CA 207

IN MEMORIAM

Adams, Robert Malcolm, Jul 23, 1974 356
Back, James B., Sep 20, 1974 448
Baldwin, L. Grant, Apr 20, 1974 166
Bandelier, Royall H., Apr 26, 1974 263
Barden, Robert Bradshaw, Sep 8, 1974 448
Barksdale, Robert W., Sep 5, 1974 448
Barnard, Harold D., Jan 17, 1974 263
Bartok, Thomas, Jun 11, 1974 263
Bilafer, Robert A., May 29, 1974 166
Bingham, Elmer McKinley, Jul 25, 1974 263
Brannon, Earl William, Jr., May 3, 1974 166
Brignoli, Walter H., May 6, 1974 166
Carlin, Gene Arnold, Aug 24, 1974 356
Chan, Raymond, Jul 5, 1974 263
Clay, Ernest H., Aug 4, 1974 356
Cline, John Wesley, Jul 10, 1974 166
Crawford, Donald J., Oct 1, 1974 532
Cunningham, Robert Arthur, Jul 21, 1974 356
Cutler, Charles Henry, Feb 7, 1974 263
Day, Harold Ellsworth, Jun 14, 1974 532
Deleray, Wilfred Louis, May 23, 1974 166
DeWitt, Foster, Apr 21, 1974 166
Dickey, Lloyd B., Jul 18, 1974 263
Draper, David H., Jun 1, 1974 166
Dubin, Hyman Mayer, Oct 2, 1974 532
Dykes, Jack, Jul 30, 1974 263
Eccleston, John Oliver, Aug 14, 1974 356
Falk, Harry L., Sep 19, 1974 448
Ferrand, Paula Thon, Oct 14, 1974 532
Fesenmaier, Otto Bernard, May 19, 1974 166
Foster, William Paul, Apr 21, 1974 166
Foulks, Charles Allison, Jr., Jul 13, 1974 263
Frame, Paul W., Sr., May 26, 1974 166
Frederickson, Sophie Henrietta, Apr 22, 1974 166
Frees, Benjamin Marsh, Sr., Aug 27, 1974 356
Frizzell, Rex Russell, May 17, 1974 166
Garetz, Michael A., May 8, 1974 166
Gentry, Richard W., May 18, 1974 166
Goldyne, Alfred Joseph, Jul 18, 1974 263
Greene, Charles Henry, Sep 28, 1974 532
Grove, Howard R., Jul 20, 1974 263
Hackett, Arthur Bailey, Aug 15, 1974 356
Haddow, Norval W., May 2, 1974 166
Hall, James Hinquong, Oct 6, 1974 532
Harris, William L., Aug 18, 1974 448
Harwick, Herbert J., Jul 31, 1974 448
Herring, Elmer Franklin, Sep 4, 1974 448
Herschel, Paul E., Oct 17, 1974 532
Hodgdon, Frank W., Jr., Jun 7, 1974 166
Hummel, Alvin Lee, Apr 28, 1974 166
Husband, Myron, Sr., May 19, 1974 167
Iki, George S., Sep 1, 1974 356
Isaak-Jantzen, Constantine John, May 9, 1974 167
Jacobs, Albert M., Mar 25, 1974 448
Johnson, Ernest D., May 29, 1974 167
Kading, Earl C., Sep 1974 532
Kennedy, Dean M., Jr., Aug 4, 1974 448
Kirtland, Howard B., Jr., Jul 10, 1974 263
Kobayashi, Norman T., Sep 4, 1974 448
Kohl, Roy Douglass, Jul 20, 1974 263
Kringel, Alan, Aug 3, 1974 356
Lachman, George S., Aug 4, 1974 356
Larus, Norman Jackson, Jun 5, 1974 263
Ledford, Roy Merl, Sr., May 6, 1974 167
Leland, Harold Galen, Sep 16, 1974 448
Lindsey, Ralph Everett, Jul 23, 1974 448

Love, Jesshill, Oct 1, 1974 532
Lovin, Bailey J., Jr., Sep 26, 1974 532
Lusby, Ralph Ward, Jan 14, 1974 167
Martin, Ivan Elwood, Jun 17, 1974 263
McGovney, Richard B., Apr 26, 1974 356
Miller, Clark R., Sep 27, 1974 532
Missner, Frank Roy, May 26, 1974 167
Moon, Henry D., Aug 2, 1974 263
Moore, Oliver Merritt, May 7, 1974 167
Morris, Roy Henry, Jun 16, 1974 167
Mosher, Walter Frederick, Jul 5, 1974 263
Murray, Dwight H., Sr., Oct 7, 1974 448
Novy, Frederick G., Jr., Oct 7, 1974 532
Oliva, George, Jr., Jul 14, 1974 264
Pandes, Jose Verdeflor, Oct 15, 1974 532
Petty, William, Oct 2, 1974 532
Piser, Alfred L., Apr 8, 1974 356
Rampoldi, Henry Darr, Jul 29, 1974 264
Ratner, Reuben, Jul 4, 1974 264
Reardan, Frank B., Jul 22, 1974 264
Roberts, James Eugene, Feb 12, 1974 264
Sable, Morris, May 10, 1974 167
Scanlon, Wilko Gruver, Sep 20, 1974 533
Searls, Henry Hunt, Jun 22, 1974 264
Shirley, Hale Foreman, Oct 7, 1974 533
Skorneck, Alan B., Apr 28, 1974 167
Snyder, William H., Jr., Jun 1, 1974 167
Spencer, James Edgar, Sep 20, 1974 533
Stafford, Clarence E., Aug 4, 1974 448
Stange, Frederick Albert, Jun 6, 1974 167
Steinbeck, Felice, Oct 1974 533
Sullivan, Cletus S., May 11, 1974 167
Sundberg, Rudolph Herbert, Aug 29, 1974 356
Sutton, Charles Edward, Jul 4, 1974 264
Taft, John Harris, Sep 28, 1974 533
Thurlow, Alfred A., Jr., May 22, 1974 167
Titcomb, Lillian Ray, May 30, 1974 167
Wachtel, Michael, Sep 17, 1974 448
Warner, Ohmer Hubert, Apr 1974 167
Warnock, Ernest Henry, Oct 1, 1974 533
Wells, Maria C., Apr 27, 1974 167
Werthmann, Paul Anthony, Sep 21, 1974 448
Williams, Anson P., Jul 5, 1974 264
Williams, Wilburn J., Jul 3, 1974 264
Wright, John Madden, Sep 7, 1974 448
Young, Maurice L., Jan 25, 1974 167

SUBJECT INDEX

A

Abdominal Aorta, see *Management of Ruptured Aneurysms*
Abscess, see *Brain*
Acupuncture Needles, see *Permanent Subcutaneous Gold*
Adenocarcinoma of the Colon and Rectum, Allan J. Wagman, William H. Kern 185
Adolescent Girls, see *Anatomical Basis for Leg Edema*
Adolescents Participating in Sports, see *Medical Aspects of*
Advances in Clinical Medicine, see *Epitomes*
Adversaries in Patient Care [Medicaid-Medi-Cal] (Editorial) 62
Allergy, Food, see *Sublingual Testing*
Allergy, Important Advances in, see *Epitomes*
Amputated Digits, see *Saving*
Anatomical Basis for Unilateral Leg Edema in Adolescent Girls, An, Mahlon C. Connett 324
Anemia, Macrocytic, see *Neutrophilic Hypersegmentation*
Aneurysm, see *Dissecting*
Anorexia Nervosa (UC, San Diego, and San Diego Veterans Administration Hospital, Psychiatric Grand Rounds), Participants: J. Hamp Atkinson, Kitty Cleveland, Robert Nemiroff, Alvin Robbins 112
Editorial, Albert J. Stunkard 138
Antiobiotic Therapy, see *Pseudomembranous Enterocolitis—Resurgence Related to*
Antidiuretic Hormone Secretion, see *Inappropriate*
Aortic Origin of Right Pulmonary Artery, see *Tricuspid Atresia*
Asbestos-Related Diseases, see *Spectrum of*
Assessment and Resuscitation of the Injured Patient, (Trauma Rounds—San Francisco General Hospital). Chief Discussant: Donald D. Trunkey 153
Atresia, see *Tricuspid*
Atrium, see *Sick Sinus*
Audit, see *Patient Care*

B

Bacteriology of the Gut and Its Clinical Implications (UC, Los Angeles [and Sepulveda and Wadsworth VA Hospitals] Interdepartmental Clinical Case Conference), Moderator: James S. Clarke; Discussants: John G. Bartlett, Sydney M. Finegold, Sherwood L. Gorbach, Samuel E. Wilson 390
Editorial, Martin H. Floch 423
Battered Child, The (Letter to Editor), Burton Sokoloff 509
Boerhaave Syndrome, see *Complications of Vomiting*

Book Reviews:

Alimentary Tract Roentgenology—2nd Ed.—Vol. 1 and 2, *Margulis & Burhenne* 172
Clinical Gynecologic Endocrinology and Infertility, *Speroff et al* 171
Dermatology—2nd Ed., *Hall-Smith et al* 170
DuVries' Surgery of the Foot—3rd Ed., *Inman* ... 171
Dyslexia, *Goldberg & Schiffman* 169
Human Radiation Biology, *Prasad* 172
Microbiology—2nd Ed., *Davis et al* 168
Peripheral Arterial Diseases, see *Vascular Surgery, Vol. 1*
Pills, Profits, and Politics, *Silverman & Lee* 168
Postoperative Disorders of the Gastrointestinal Tract, *Wright & Tilson* 172
Surgical Pathology—5th Ed., *Ackerman & Rosai* .. 169
Tumors of the Head and Neck, *Batsakis* 171
Uppers and Downers, *Smith & Wesson* 168
Vascular Surgery—Vol. 1—Peripheral Arterial Diseases, *Cranley* 168

Brain Abscess (UC, Los Angeles, and Harbor General Hospital Teaching Conference), Moderator: Thomas T. Yoshikawa; Participants: Stanley J. Goodman, Thomas T. Yoshikawa 207
Editorial, Kemp Clark 229
Bran, see *More on*

C

Calcium Homeostasis, see *Metabolism*
Calcium Homeostasis, see *Vitamin D and*
California, see *Occupational Health*
California, see *Tick-Bite in Oregon*

California Medical Association:

Occupational Health—Status of Governmental and Legal Control in California, Committee on Occupational Health 161
Proposed Constitutional Amendments for Action in 1975 358
and December issue, CMA Annual Session Program, page 31

Cancer, Thyroid, see *Thyroid Nodules*
Cardiac Valve Replacement—The Rationale for Earlier Operation, Joseph S. Carey, William G. Plested, Calvin Scott 327
Editorial, Albert Starr 319
Cardiovascular Institute, UCSF, see *Specialty Conferences*
Child, see *Battered*
[Child Abuse], see *Battered Child*
Child Abuse, see *Duty to Report*
Child Abuse, see *Malpractice Liability*
Children, see *Urinary Tract Infections*
Chinese Herbal Medicines (FDA Drug Bulletin) .. 261
Chronic Leg Ulceration in a Patient with Leprosy, Joel M. Noe, Joan Barber 430
Clergy and Patient Care, The (Editorial) 498
Clindamycin Colitis—An Emerging Problem, William D. Carey, Martin Brotman 504
Clinical Medicine, Advances in, see *Epitomes*
Colitis, see *Clindamycin*
Colitis, see *Pseudomembranous*
Colon, see *Adenocarcinoma of*
Colon, see *Pressure in*
Colonoscopic Polypectomy, see *Non-Invasive*
Compensating Victims of Violent Crime (Information), Gilbert Geis 161
Complications of Vomiting—The Boerhaave and the Mallory Weiss Syndromes (Medical Staff Conference) 50
Conchs, see *Vibrio Parahaemolyticus*
Conference on the Pathophysiology of Diabetes Mellitus (Notes from Important or Unusual Meetings), Donald E. McMillan, Peter Amacher 350
Editorial, Rachmiel Levine 426
Consensus at Last, A (Editorial), Calvin M. Kunin 421
Constitutional Amendments, see *Proposed*
Correction of Rectal Prolapse by Anterior Resection, Cary L. Conyers, P. Kent Cullen, Jr. 270
Critical Masses in the Distribution of Health Care Services (Editorial) 136
Letter to Editor, Marvin J. Shapiro 328
Crime, see *Compensating Victims of Violent*

D

Developing Regional Network Residency Program in Family Practice, A (Medical Education), John P. Geyman, Thomas C. Brown 514
Diabetes Mellitus, see *Conference on the Pathophysiology*
Diabetic Microangiopathy (Medical Staff Conference) 404
Disc Lesion Management (Letter to Editor), J. H. Kennedy 152
Dissecting Aneurysm (Medical Staff Conference) .. 482
[Drugs] for Travel, see *Simple Kit*
Duty to Report Child Abuse (Editorial), C. Henry Kempe 229
Dysenteriae Type 1, see *Shigella*

E

Editorials:

Adversaries in Patient Care [Medicaid-Medi-Cal] .. 62
Brain Abscess, Kemp Clark 229
Cardiac Valve Replacement—Rationale for Earlier Operation, Albert Starr 319
Clergy and Patient Care, The 498
Consensus at Last, A [Urinary Tract Infection], Calvin M. Kunin 421
Critical Masses in the Distribution of Health Care Services 136
Letter to Editor, Marvin J. Shapiro 328
Duty to Report Child Abuse, C. Henry Kempe ... 229
Emergency Medicine 422
Fascinations and Frustrations of Diabetes Mellitus, Rachmiel Levine 426
Gallium-67 Broad Spectrum Diagnostic?, Paul B. Hoffer 137
Human Gut Microecology, Martin H. Floch 423
Impact of Recent Findings Concerning Vitamin D Metabolism on Clinical Medicine, H. F. DeLuca . 64
Letter to Editor, Anthony W. Norman, Jack W. Coburn, David L. Hartenbower 508
Inappropriate versus Appropriate Antidiuretic Hormone Secretion, Robert W. Schrier 62
Levodopa after Five Years, Phillip D. Swanson ... 220
Myelomeningocele, Rodney K. Beals 321
National Health Insurance—An Opportunity for a New Approach 322
New Hope for an Old Ill—Anorexia Nervosa, Albert J. Stunkard 138
On Training Health Manpower for Primary Care .. 498
Patient Care Audit 426
Pseudomembranous Colitis, Francis J. Tedesco, David H. Alpers 499
Reaching the Unreached with Health Care 230
Sicknesses of the Sinus Node, Thomas N. James .. 496
Thyroid Nodules and Thyroid Cancer, Monte A. Greer 425
Top Flight Brains for Medicine [Premedical Students] 65
WAMI 320

Electromyography, see *More on*
Emergency Medicine (Editorial) 422
Enterocolitis, see *Pseudomembranous*
[Environmental Health], see *Spectrum of Asbestos-Related Diseases*

Epitomes of Progress in Clinical Medicine:

Allergy 55
Physical Medicine and Rehabilitation 131
General Surgery 220
General and Family Practice 313
Preventive Medicine and Public Health 413
Plastic Surgery 490

Epidemiology of Influenza in California, 1968-1973, The, James Chin, Robert L. Magoffin, Edwin H. Lennette 94
Evaluation of the Patient with Head Injury (Trauma Rounds—San Francisco General Hospital), Chief Discussant: Julian Hoff 435

Evidence of Skeletal Muscle Involvement in Psittacosis, Peter Sullivan, Austin Brewin 232

F

Family Physician, see *What Is So Special About*
Family Practice, see *Developing Regional Network Residency Program in*
Family Practice, Important Advances in, see *Epitomes*
Fascinations and Frustrations of Diabetes Mellitus (Editorial), Rachmiel Levine 426

FDA Drug Bulletin—Selected Items:
Chinese Herbal Medicines 261

Fingers, see *Saving Amputated Digits*
Food Allergy, see *Sublingual Testing*

G

Gallium-67 Broad Spectrum Diagnostic? (Editorial), Paul B. Hoffer 137
Gallium-67 Scans in the Diagnosis of Pyelonephritis, Warren O. Kessler, Ruben F. Gittes, Sheldon R. Hurwitz, Joseph P. Green 91
Editorial, Paul B. Hoffer 137
Gastroenteritis, see *Seminars in Infectious Disease*
Gastroenteritis, see *Vibrio Parahaemolyticus*
General Practice, Important Advances in, see *Epitomes*
General Surgery, Important Advances in, see *Epitomes*
Girls, Adolescent, see *Anatomical Basis for Leg Edema*
Girls, Young, see *Urinary Tract Infections*
Gold Acupuncture Needles, see *Permanent Subcutaneous*
Government and Legal Control, see *Occupational Health*

Government and Medicine:
Medi-Cal—Another Way, James G. Roney, Jr. 83
Guideposts in the RMP Odyssey, The, Caspar W. Weinberger 158

Granulomatosis, see *Wegener's*
Group Practice Approach to Rural Community Mental Health (The Health Care Team), Noel Guillozet 249
Editorial 230
Guideposts in the RMP Odyssey, The (Government and Medicine), Caspar W. Weinberger 158
Gut, see *Bacteriology of*
Gut Microecology, see *Human*

H

Hands, see *Saving Amputated Digits*
Harbor General Hospital, see *Specialty Conferences*
Head Injury, see *Evaluation of the Patient with*
Health Care, see *Critical Masses*
Health Care, see *Reaching the Unreached*

Health Care Team:
Group Practice Approach to Rural Community Mental Health, Noel Guillozet 249
Editorial 230

Health Insurance, see *National*
Health Manpower, see *On Training*
Heat Stroke (Medical Staff Conference) 302
Herbal Medicines, see *Chinese*
Heroin and Methadone Addiction, see *Use of Propoxyphene*
Homeostasis, Calcium, see *Vitamin D and*
Hormone Secretion, Antidiuretic, see *Inappropriate*
Hospital, see *Quality of Care*
Human Gut Microecology (Editorial), Martin H. Floch 423

I

Infectious Gastroenteritis, see *Seminars in Infectious Disease*
Impact of Recent Findings Concerning Vitamin D Metabolism on Clinical Medicine, The (Editorial), H. F. DeLuca 64
Letter to Editor, Anthony W. Norman, Jack W. Coburn, David L. Hartenbower 508
Important Advances in Clinical Medicine, see *Epitomes*
Inappropriate Secretion of Antidiuretic Hormone (UC, San Diego, and University Hospital of San Diego County, Pediatric Grand Rounds), Participants: Stanley A. Mendoza, Margaret Keller .. 45
Editorial, Robert W. Schrier 62
Inappropriate versus Appropriate Antidiuretic Hormone (Editorial), Robert W. Schrier 62

Information:
Bulletin on Drugs, see *FDA Drug Bulletin*
Compensating Victims of Violent Crime, Gilbert Geis 161
Occupational Health—Status of Governmental and Legal Control in California, CMA Committee on Occupational Health 161

Informed Commentary, see *Informed Opinion*

Informed Opinion:
Medical Manpower in Oregon, Alexander R. Gassaway 254

Influenza in California, see *Epidemiology of*
International Health—Report of the 27th World Health Assembly of the World Health Organization, Geneva, Switzerland, May 7-24, 1974 (Notes from Important or Unusual Meetings), Francis W. Parnell 349
Intestine, see *Nonocclusive Hemorrhagic Necrosis*
Ischemia, see *Organ*

J

Joints, see *Practical Aspects of Synovial Fluid Aspiration*

K

Kidney Disease—Program, see *Medical Audit*
Kroc Foundation, see *Conference on Pathophysiology of Diabetes Mellitus*

L

Leg Edema, see *Anatomical Basis*
Leg Ulceration, see *Chronic*
Legg-Calvé-Perthes Disease (Letter to Editor), Elmer E. Specht, Howard Barkan 150
Leprosy, see *Chronic Leg Ulceration in a Patient with*

Letters to Editor:

Acupuncture Needles, see *Permanent*
Battered Child, The, Burton Sokoloff 509
Critical Masses in Health Care, Marvin J. Shapiro . 328
Disc Lesion Management, J. H. Kennedy 152
Early and Periodic Screening, Howard F. Long ... 235
Legg-Calvé-Perthes Disease, Elmer E. Specht, Howard Barkan 150
Localization of a Parathyroid Adenoma by Thermography, Eugene C. Wasson III, John L. Smith, James A. Usselman 144
Letter to Editor, Jorge A. Franco 328
More on Bran, S. Berkowitz 151
More on Electromyography 237
Ernest W. Johnson 237
William J. Lajoie 238
Paul H. Goodley 239
Nocardia Asteroides Infections, James A. Krick, Jack S. Remington 235
Reply, Ervin Epstein 236
Organ Ischemia, Stephan A. Sacks 433
Author Replies, Rex L. Jamison 434
Permanent Acupuncture Needles, Willard E. Goodwin 328
Position on Early and Periodic Screening, Martin M. Gershman 69
Letter to Editor, Howard F. Long 235
Pressure in the Colon, E. Fritz Schmerl 151
Semi-Retired Physicians, Reinhard J. Bachrach ... 508
Simple [Drug] Kit for Travel, Wayne P. Chesbro .. 327
Sublingual Testing in the Diagnosis of Food Allergy, Douglas C. Heiner 152
Tick-Borne Diseases, Glenn C. Szalay 328
Tricuspid Valve Replacement, Jerome Harold Kay . 70
Twelve-Year Survival of a Patient with Letterer-Siwe's Disease, William W. Johnson 433
Vitamin D and Calcium Homeostasis, Anthony W. Norman, Jack W. Coburn, David L. Hartenbower 508

Letterer-Siwe's Disease, see *Twelve-Year Survival*
Leukemia, Acute Granulocytic, see *Neurological Manifestations*
Levodopa After Five Years (Editorial), Phillip D. Swanson 228
Levodopa, see *Parkinson's Disease*
Liver Trauma, see *Management of*
Localization of a Parathyroid Adenoma by Thermography (Letter to Editor), Eugene C. Wasson III, John L. Smith, James A. Usselman 144
Letter to Editor, Jorge A. Franco 328
Lung, see *Superinfections of*

M

Macrocytic Anemia, see *Neutrophilic Hypersegmentation*
Mallory-Weiss Syndrome, see *Complications of Vomiting*
Malpractice Liability for Failing to Report Child Abuse (Medical Jurisprudence), Richard J. Kohlman 244
Editorial, C. Henry Kempe 229
Letter to Editor, Burton Sokoloff 509
Management of Liver Trauma (Trauma Rounds—San Francisco General Hospital), Chief Discussant: Walter Ballinger 329
Management of Pancreatic Injuries (Trauma Rounds—San Francisco General Hospital), Chief Discussant: Muriel Steele 240
Management of Ruptured Aneurysms of the Abdominal Aorta (Trauma Rounds—San Francisco General Hospital), Chief Discussant: Edwin J. Wylie 71
Manpower, see *Medical*
[Medicaid-Medi-Cal], see *Adversaries in*
Medi-Cal—Another Way (Government and Medicine), James G. Roney, Jr. 83
Medical Aspects of Adolescents Participating in Sports, Samuel Hurwitz 443
Medical Audit in Action—Experience in a Regional Kidney Disease Program [PSRO], (Progress in Public Accountability), Benjamin H. Barbour, Mark C. Lambert, Stan R. Fisher 439
Editorial 426

Medical Education:

WAMI [Washington, Alaska, Montana, Idaho]—An Experiment in Regional Medical Education, M. Roy Schwarz 333
Editorial 320
Developing Regional Network Residency Program in Family Practice, A, John P. Geyman 514

Medical Manpower in Oregon (An Informed Commentary), Alexander R. Gassaway 254

Medical Jurisprudence:

Malpractice Liability for Failing to Report Child Abuse, Richard J. Kohlman 244
Editorial, C. Henry Kempe 229
Letter to Editor, Burton Sokoloff 509

Medical Opinion:

Myth of Sickle Cell Trait, Lonnie R. Bristow 77

Medical Progress:

Metabolism and Action of the Hormone Vitamin D—Its Relation to Diseases of Calcium Homeostasis, Jack W. Coburn, David L. Hartenbower, Anthony W. Norman 22
Editorial, H. F. DeLuca 64
Letter to Editor, Anthony W. Norman, Jack W. Coburn, David L. Hartenbower 508
Parkinson's Disease and Levodopa—A Five-Year Follow-up and Review, Charles H. Markham, Leo J. Treciokas, Shirley G. Diamond 188
Editorial, Phillip D. Swanson 228
Pseudomembranous Enterocolitis—Resurgence Related to Newer Antibiotic Therapy, Emmet B. Keeffe, Ronald M. Katon, Tsoi T. Chan, Clifford S. Melnyk, John A. Benson, Jr. 462
Editorial, Francis J. Tedesco, David H. Alpers .. 499

Medical Staff Conferences:

Complications of Vomiting—The Boerhaave and the Mallory-Weiss Syndromes, Chief Discussant: H. David Watts 50
Wegener's Granulomatosis, Chief Discussant: David S. Gullion 123
Heat Stroke, Chief Discussant: Floyd C. Rector, Jr. 302
Diabetic Microangiopathy, Chief Discussant: Martin D. Siperstein 404
Dissecting Aneurysm, Chief Discussant: John R. Stoner 482

Medicine, Clinical, Advances, see *Epitomes*

Mental Health, Rural Community, see *Group Practice Approach*
Metabolism and Action of the Hormone Vitamin D —Its Relation to Diseases of Calcium Homeostasis (Medical Progress), Jack W. Coburn, David L. Hartenbower, Anthony W. Norman 22
Editorial, H. F. DeLuca 64
Letter to Editor, Anthony W. Norman, Jack W. Coburn, David L. Hartenbower 508
Methadone Addiction, see *Use of Propoxyphene Napsylate*
Microangiopathy, see *Diabetic*
More on Bran (Letter to Editor), S. Berkowitz ... 151
More on Electromyography (Letters to the Editor), Ernest W. Johnson; William J. Lajoie; Paul H. Goodley 237
Myelomeningocele (Editorial), Rodney K. Beals .. 321
Myelomeningocele—A Symposium on Orthopedic, Ophthalmologic, Urologic, Psychological and Social, Neurosurgical and General Considerations (UC, San Francisco Pediatric Rounds) 281
1. Orthopedic Management in Children, Elmer E. Specht 281
2. Ophthalmologic Problems, Ernest K. Goodner 291
3. Urologic Considerations, Emil A. Tanagho .. 292
4. Psychosocial Problems and Social Work Interventions, Barbara Prince 297
5. Neurosurgical Aspects, Byron C. Pevehouse .. 298
6. General Considerations, Peter Cohen 300
Editorial, Rodney K. Beals 319

Myth of Sickle Cell Trait, The (Medical Opinion), Lonnie R. Bristow 77

N

National Health Insurance—An Opportunity for a New Approach (Editorial) 322
Neurological Considerations, see *Myelomeningocele*
Neurological Manifestations of Acute Granulocytic Leukemia, S. A. Armentrout, R. F. Ulrich 1
Neurotophilic Hypersegmentation Without Macrocytic Anemia, Paul G. Hattersley, Judith L. Engels 179
New Hope for an Old Ill—Anorexia Nervosa (Editorial), Albert J. Stunkard 138
Nocardia Asteroides Infections (Letter to Editor), James A. Krick, Jack S. Remington 235
Reply, Ervin Epstein 236
Nonocclusive Hemorrhagic Necrosis of the Intestine, Sheldon E. Cohen, Martin I. Feldman, Earl F. Wolfman, Jr. 449
Non-Invasive Colonoscopic Polypectomy—Review of 100 Cases, Joel F. Panish, George Berci 6
Non-Refluxing Ureters, see *Urinary Tract Infections*

Notes from Important or Unusual Meetings:

Conference on the Pathophysiology of Diabetes Mellitus, Donald E. McMillan, Peter Amacher 350
Editorial, Rachmiel Levine 426
International Health—Report of the 27th World Health Assembly of the World Health Organization, Geneva, Switzerland, May 7-24, 1974, Francis W. Parnell 349

O

Occupational Health—Status of Governmental and Legal Control in California, CMA Committee on Occupational Health 161
On Training Health Manpower for Primary Care (Editorial) 495
Ophthalmological Considerations, see *Myelomeningocele*
Oregon, see *Medical Manpower*
Oregon, see *Tick-Bite in*
Organ Ischemia (Letter to Editor), Stephan A. Sacks 433
Author Replies, Rex L. Jamison 434
Orthopedic Management, see *Myelomeningocele*

P

Pancreatic Injuries, see *Management of*
Paralysis, see *Tick-Bite in Oregon*
Parathyroid Adenoma, see *Localization of*
Parathyroid Adenoma, see *Thermography to Localize*
Parkinson's Disease and Levodopa—A Five-Year Follow-up and Review (Medical Progress), Charles H. Markham, Leo J. Treciokas, Shirley G. Diamond 188
Editorial, Phillip D. Swanson 228
Patient Care, see *Clergy and*
Patient Care Audit (Editorial) 426

Pediatric Rounds:

Myelomeningocele—A Symposium on Orthopedic, Ophthalmologic, Urologic, Psychological and Social, Neurosurgical and General Considerations (UC, San Francisco): 281
1. Orthopedic Management in Children, Elmer E. Specht 281
2. Ophthalmologic Problems, Ernest K. Goodner 291
3. Urologic Considerations, Emil A. Tanagho .. 292
4. Psychosocial Problems and Social Work Interventions, Barbara Prince 297
5. Neurosurgical Aspects, Byron C. Pevehouse .. 298
6. General Considerations, Peter Cohen 300
Editorial, Rodney K. Beals 319

Penetrating Thoracic Trauma (Trauma Rounds—San Francisco General Hospital), Chief Discussant: Arthur N. Thomas 510
Periodic Screening, see *Position*
Permanent Acupuncture Needles (Letter to Editor), Willard E. Goodwin 328
Permanent Subcutaneous Gold Acupuncture Needles, Barry B. Behrstock, Nicholas L. Petrakis 140
Letter to Editor, Willard E. Goodwin 328
Physician, Family, see *What Is So Special About a*
Physical Medicine, Important Advances in, see *Epitomes*
Plastic Surgery, Important Advances in, see *Epitomes*
Polypectomy, see *Non-Invasive*
Position on Early and Periodic Screening (Letter to Editor), Martin Gershman 69
Letter to Editor, Howard F. Long 235
Practical Aspects of Synovial Fluid Aspiration—The Approaches to Major Extremity Joints and Examination of the Aspirate, Marvin H. Meyers 100
Premedical Students, see *Top Flight Brains*
Pressure in the Colon (Letter to the Editor), E. Fritz Schmerl 151

Preventive Medicine, Important Advances in, see *Epitomes*
Primary Care, see *On Training . . . for*
Pseudomembranous Colitis (Editorial), Francis J. Tedesco 499

Progress in Public Accountability:

Quality of Care and Utilization Assessment—The Hospital Response to PSRO, Woodbury Perkins . 342
Medical Audit in Action—Experience in a Regional Kidney Disease Program [PSRO], Benjamin H. Barbour, Mark C. Lambert, Stan Fisher 439
Editorial 426

Proposed Constitutional Amendments for Action in 1975 (CMA) 358
and December issue, CMA Annual Session Program, page 31
Propoxyphene Napsylate, see *Use of*
Pseudomembranous Enterocolitis—Resurgence Related to Newer Antibiotic Therapy (Medical Progress), Emmet B. Keeffe, Ronald M. Katon, Tsoi T. Chan, Clifford S. Melnyk, John A. Benson, Jr. 462
Editorial, Francis J. Tedesco, David H. Alpers .. 499
Psittacosis, see *Evidence of Skeletal Muscle Involvement*
[PSRO], see *Medical Audit*
PSRO, see *Quality of Care*

Psychiatric Grand Rounds:

Anorexia Nervosa (UC, San Diego, and San Diego Veterans Administration Hospital), Participants: J. Hamp Atkinson, Kitty Cleveland, Robert Nemiroff, Alvin Robbins 112
Editorial, Albert J. Stunkard 138

Psychological Considerations, see *Myelomeningocele*
Public Health, Important Advances in, see *Epitomes*
Pyelonephritis, see *Gallium-67 Scans in the Diagnosis of*

Q

Quality of Care and Utilization Assessment—The Hospital Response to PSRO (Progress in Public Accountability), Woodbury Perkins 342

R

Radiologic Aspects, see *Urinary Tract Infections*
Reaching the Unreached with Health Care (Editorial) 230
Rectal Prolapse, see *Correction of*
Rectum, see *Adenocarcinoma of the Colon*
Refluxing Ureters, see *Urinary Tract Infections*
Regional Medical Education, see *WAMI*
Regional . . . Program, see *Medical Audit*
[Regional Medical Programs], see *Guideposts in the RMP Odyssey*
Regional Network Residency Program in Family Practice, see *Developing*
Rehabilitation, Important Advances in, see *Epitomes*
Residency Program in Family Practice, see *Developing*
Retired Physicians, see *Semi-*
Rural Community, see *Group Practice Approach to*

S

San Diego VA Hospital, see *Specialty Conferences*
San Francisco General Hospital, see *Specialty Conferences*
San Francisco General Hospital, see *Trauma Rounds*
Saving Amputated Digits—Current Status of Replantation of Fingers and Hands, Gary K. Frykman, Virchel E. Wood 265
Screening, see *Position on Early*
Seminars in Infectious Disease—A New Look at Infectious Gastroenteritis, Joseph W. St. Geme, Jr. 456
Semi-Retired Physicians (Letter to Editor), Reinhard J. Bachrach 508
Sepulveda VA Hospital, see *Bacteriology of the Gut*
Shigella Dysenteriae Type 1—Severe Dysentery and Sepsis with Hematologic, Hepatic and Renal Complications, Victor D. Levine, Gary D. Overturf, Allen W. Mathies 501
Sick Sinus and Ailing Atrium, The (UC, San Francisco, Cardiovascular Institute, and San Francisco General Hospital Teaching Conference), Melvin M. Scheinman, Robert Peters, David S. Hirschfeld, Joseph A. Abbott, Fred Kunkel 473
Editorial, Thomas N. James 496
Sickle Cell Trait, see *Myth of*
Sicknesses of the Sinus Node (Editorial), Thomas N. James 496
Simple [Drug] Kit for Travel, A (Letter to Editor), Wayne P. Chesbro 327
Sinus Node, see *Sicknesses of*
Sinus, see *Sick*
Social Considerations, see *Myelomeningocele*

Special Articles:

Medical Aspects of Adolescents Participating in Sports, Samuel Hurwitz 443
What Is So Special About a Family Physician?, Joseph B. Deisher 521

Specialty Conferences:

Inappropriate Secretion of Antidiuretic Hormone (UC, San Diego, and University Hospital of San Diego County), Participants: Stanley A. Mendoza, Margaret Keller 45
Anorexia Nervosa (UC, San Diego, and San Diego Veterans Administration Hospital Psychiatric Rounds), Participants: J. Hamp Atkinson, Kitty Cleveland, Robert Nemiroff, Alvin Robbins 112
Editorial, Albert J. Stunkard 138
Brain Abscess (UC, Los Angeles, and Harbor General Hospital Teaching Conference), Moderator: Thomas T. Yoshikawa; Participants: Stanley J. Goodman, Thomas T. Yoshikawa 207
Editorial, Kemp Clark 229
Myelomeningocele—A Symposium on Orthopedic, Ophthalmologic, Urologic, Psychological and Social, Neurosurgical and General Considerations (UC, San Francisco Pediatric Rounds): 281
1. Orthopedic Management in Children, Elmer E. Specht 281
2. Ophthalmologic Problems, Ernest K. Goodner 291
3. Urologic Considerations, Emil A. Tanagho .. 292
4. Psychosocial Problems and Social Work Interventions, Barbara Prince 297
5. Neurosurgical Aspects, Byron C. Pevehouse .. 298
6. General Considerations, Peter Cohen 300
Editorial, Rodney K. Beals 319

Bacteriology of the Gut and Its Clinical Implications (UC, Los Angeles Interdepartmental Clinical Case Conference), Moderator: James S. Clarke; Discussants: John G. Bartlett, Sydney M. Finegold, Sherwood L. Gorbach, Samuel E. Wilson .. 390
Editorial, Martin H. Floch 423
Sick Sinus and Ailing Atrium, The (UC, San Francisco, Cardiovascular Institute, and San Francisco General Hospital Teaching Conference), Melvin M. Scheinman, Robert Peters, David S. Hirschfeld, Joseph A. Abbott, Fred Kunkel 473
Editorial, Thomas N. James 496

Spectrum of Asbestos-Related Diseases, The, William N. Rom, Philip E. S. Palmer 10
Sports, see *Medical Aspects of Adolescents*
Stupor, Bradycardia, Hypotension and Hypothermia —A Presentation of Wernicke's Encephalopathy with Rapid Response to Thiamine, William J. Ackerman 428
Sublingual Testing in the Diagnosis of Food Allergy (Letter to Editor), Douglas C. Heiner 152
Superinfections of the Lung—An Evaluation by Serial Transtracheal Aspirations, E. Jack Benner, Jurg P. Munzinger, Richard Chan 173
Surgery, General, see *Epitomes*
Symposium, see *Myelomeningocele*

T

Testing, see *Sublingual*
Thermography to Localize Parathyroid Adenoma (Letter to Editor), Jorge A. Franco 328
Thoracic Trauma, see *Penetrating*
Thyroid Nodules and Thyroid Cancer, Francis S. Greenspan 359
Editorial, Monte A. Greer 425
Tick-Bite in Oregon: Paralysis in California, Richard W. Emmons, F. Michael Brewster, Bernard C. Nelson 142
Letter to Editor, Glenn C. Szalay 328
Tick-Borne Diseases (Letter to Editor), Glenn C. Szalay 328
Top Flight Brains for Medicine [Premedical Students] (Editorial) 65
Transtracheal Aspirations, see *Superinfections*

Trauma Rounds:

Management of Ruptured Aneurysms of the Abdominal Aorta, Chief Discussant: Edwin J. Wylie 71
Assessment and Resuscitation of the Injured Patient, Chief Discussant: Donald D. Trunkey 153
Management of Pancreatic Injuries, Chief Discussant: Muriel Steele 240
Management of Liver Trauma, Chief Discussant: Walter Ballinger 329
Evaluation of the Patient with Head Injury, Chief Discussant: Julian Hoff 435
Penetrating Thoracic Trauma, Chief Discussant: Arthur N. Thomas 510

Travel Kit [Drugs], see *A Simple*
Treatment of Ureterovesical Reflux, see *Urinary Tract Infections*
Tricuspid Atresia and Aortic Origin of Right Pulmonary Artery in a Nine-Year-Old Girl, Lawrence L. Menzer, Masato Takahashi 147
Tricuspid Valve Replacement (Letter to Editor), Jerome Harold Kay 70
Twelve-Year Survival of a Patient with Letterer-Siwe's Disease (Letter to Editor), William W. Johnson 433

U

UC, Los Angeles, see *Specialty Conferences*
UC, San Diego, see *Specialty Conferences*
UC, San Francisco, see *Medical Staff Conferences*
UC, San Francisco, see *Pediatric Rounds*
UC, San Francisco, see *Specialty Conferences*
UC, San Francisco, see *Trauma Rounds*
University Hospital of San Diego County, see *Specialty Conferences*
Ureterovesical Reflux, see *Urinary Tract Infections*
Ureters, Non-Refluxing and Refluxing, see *Urinary Tract Infections*
Urinary Tract Infections in Children:
Young Girls with Non-Refluxing Ureters, William R. Fair, Duncan E. Govan, Gerald W. Friedland, Roy A. Filly 366
Radiologic Aspects, Roy Filly, Gerald W. Friedland, Duncan E. Govan, William R. Fair 374
Treatment of Ureterovesical Reflux, Duncan E. Govan, William R. Fair, Gerald W. Friedland, Roy A. Filly 382
Editorial, Calvin M. Kunin 421
Urological Considerations, see *Myelomeningocele*
Use of Propoxyphene Napsylate in the Treatment of Heroin and Methadone Addiction, The, Darryl S. Inaba, George R. Gay, Craig A. Whitehead, John A. Newmeyer, Dan Bergin 106
Utilization, see *Quality of Care*

V

Valve Replacement, see *Cardiac*
Valve Replacement, see *Tricuspid*
Veterans Administration Hospital, Wadsworth and Sepulveda, see *Bacteriology of the Gut*
Vibrio Parahaemolyticus Gastroenteritis from Eating Conchs, Frank S. Rhame, S. Benson Werner 66
Vitamin D, see *Impact of Recent Findings*
Vitamin D, see *Metabolism*
Vitamin D and Calcium Homeostasis (Letter to Editor), Anthony W. Norman, Jack W. Coburn, David L. Hartenbower 508

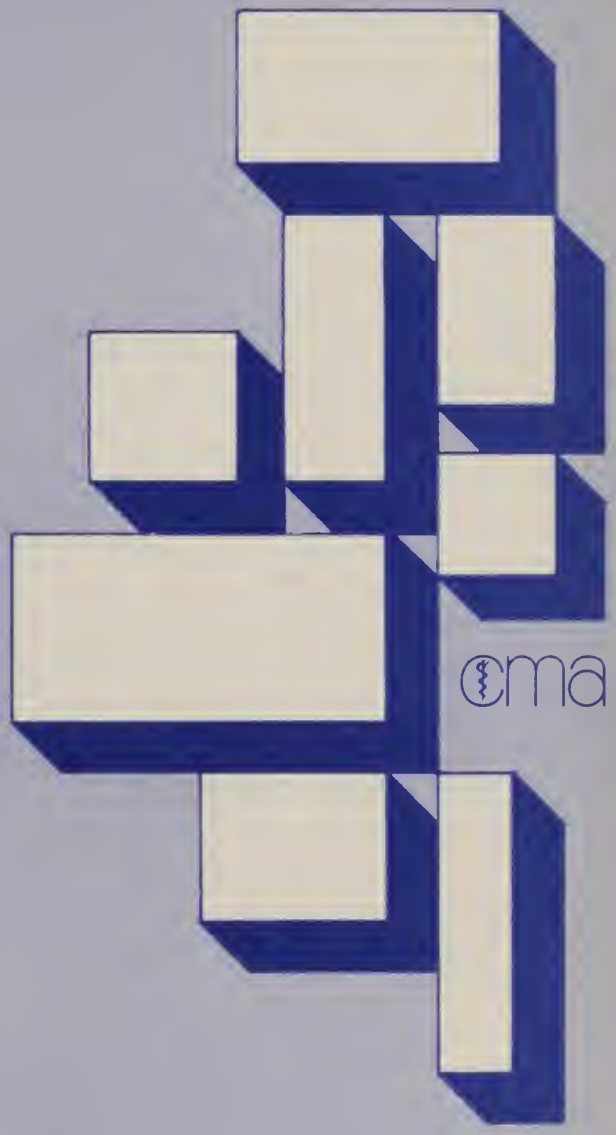
W

Wadsworth VA Hospital, see *Bacteriology of the Gut*
WAMI [Washington, Alaska, Montana, Idaho]—An Experiment in Regional Medical Education (Medical Education), M. Roy Schwarz 333
Editorial 320
Wegener's Granulomatosis (Medical Staff Conference) 123
Wernicke's Encephalopathy with Rapid Response to Thiamine, see *Stupor, Bradycardia*
What Is So Special About a Family Physician?, Joseph B. Deisher 521
World Health Organization, Report of the 27th World Health Assembly of, see *International Health*

Y

Young Girls with Non-Refluxing Ureters, see *Urinary Tract Infections in Children*

104TH ANNUAL SESSION OF THE CALIFORNIA MEDICAL ASSOCIATION FEBRUARY 21-26, 1975/LOS ANGELES



Contents

Information 4

CMA Certification Announcement 4

Out of State Guests 5

Special Conferences
- Federated Meeting 6
- The Physician and CalOSHA 6
- Cancer: A Potpourri of Progress 7
- Third Congress on Health of the School-Age Child 7
- Alcoholism and Other Drug Dependencies: The Physician's Responsibility 7
- VD Task Force Reports 8
- Physicians and Clergy Look at Homosexuality 8
- Current Pharmacology for the Practitioner 8
- Keeping Abreast of the RVS 8
- Nuclear Energy and the Public Health 8
- New Congress—New National Health Insurance Plans 9
- Your Computer vs Theirs 9
- Ambulatory Care Review 9

Specialty Section Meetings
- Allergy 10
- Anesthesiology 11
- Chest Diseases 12
- Dermatology 12
- General and Family Practice 13
- General Surgery 14
- Industrial Medicine and Surgery 14
- Internal Medicine 15
- Neurology 16
- Nuclear Medicine 16
- Obstetrics and Gynecology 16
- Ophthalmology 17
- Orthopaedics 17
- Otolaryngology 18
- Pathology 19
- Pediatrics 19
- Physical Medicine and Rehabilitation 20
- Plastic Surgery 21
- Preventive Medicine and Public Health 21
- Psychiatry 22
- Radiology 22
- Urology 22

Preregistration Forms 23

Application for Hotel Accommodations 25

Officers and Delegates 26

House of Delegates 26

District Delegations and Chairmen 28

House of Delegates Agenda 30

Proposed CMA Constitutional Amendments 31

Woman's Auxiliary 32

ACKNOWLEDGMENT

The Committee on Scientific Assemblies acknowledges the hard work and fine cooperation of the section program planners and the members of the 21 Advisory Panels in the development of the 1975 Scientific Assembly.

This annual assembly represents an opportunity for those from all specialties to meet and discuss issues of overlapping or common interest and to participate in educational programs designed especially for their needs.

The continual improvement in the educational quality of the programs is most gratifying to the Scientific Board and to the full membership of the California Medical Association.

ALBERT D. HALL, MD, *Chairman*
Committee on Scientific Assemblies
of the Scientific Board

PROGRAM

CALIFORNIA MEDICAL ASSOCIATION

104th

Annual Session

and

4th Western Scientific Assembly

February 21-26, 1975

Biltmore Hotel
and
Los Angeles Convention Center
Los Angeles

- Specialty Section Programs
- Special Conferences
- Scientific and Technical Exhibits
- Meetings of the House of Delegates

Information

PLEASE NOTE

All meeting room assignments, not available at press time, will appear in the Annual Session Handprogram.

BADGES

It is important that badges be worn at all times. Admission to all meetings and exhibits is by badge only.

COUNCIL

The Council will meet on Friday; time and location to be announced. Executive sessions will be posted on the hotel schedule boards.

HOUSE OF DELEGATES

For meeting times, places and agenda—see page 26.

MESSAGE CENTER

Provided through the courtesy of Pacific Telephone Company.

Los Angeles Convention Center—Lobby, North Wall
(213) 741-2193
9:00 am to 5:00 pm, Friday-Monday

Biltmore Hotel—Galeria
(213) 629-6416
9:00 am to 5:00 pm, Saturday-Wednesday

The Association will attempt to transmit emergency messages to individual physicians. Each physician should notify his own office of the exact times and locations of meetings he plans to attend.

Routine messages will be kept at the Message Centers. Physicians are requested to check with the Message Center at least once daily.

EXHIBITS

Technical and Scientific and Organizational Exhibits are located in the Convention Center.

INFORMATION DESK

The information desk will be located in the Convention Center Lobby near the CMA Registration Booth, and will be open daily from 9:00 am to 5:00 pm, Friday-Monday.

REGISTRATION

Registration will take place in the Convention Center Lobby, starting Friday, February 21 through Monday, February 24, 9:00 am to 5:00 pm.

All members, guests and visitors are requested to register immediately on arrival.

Admission to the conferences and section meetings, as well as to the exhibit area, is by badge only.

Members wishing to vote in specialty sections must indicate the appropriate section when registering; voting in other sections will not be allowed.

QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION

All MDs with credentials showing that they hold a valid license to practice medicine (e.g., membership card in CMA, AMA or county medical society).

Medical students upon presentation of credentials from their medical schools, letters from dean's office, or membership card in CMA, AMA or SAMA.

Medical assistants upon presentation of letter from a physician-employer or AAMA membership card.

Military paramedical personnel upon presentation of a letter from their commanding officer.

Dentists (DDS); Doctors of Veterinary Medicine (DVM); registered nurses (RN); student nurses, x-ray technicians; allied public health personnel and others will be admitted provided they have proper identification.

ALL QUESTIONS ON ADMISSION will be passed upon by a member of the Committee on Registration present at the desk.

SHUTTLE BUS

There will be continuous shuttle bus service between the Los Angeles Convention Center and the Biltmore Hotel during the hours when meetings are in progress.

SPECIAL ANNOUNCEMENT

Each scientific program which is acceptable for Category I (formal) credit toward CMA's Certificate in Continuing Medical Education is so designated:

Acceptable for Category I Credit in the CMA Certification Program

The majority of the other educational and scientific programs are acceptable for informal credit. Physicians should list on the certification reporting form the number of program hours attended. Forms and further information are available at the CMA Continuing Medical Education Booth in the exhibit area. Plan to stop by.

IMPORTANT ELECTION NOTICE TO ALL CMA MEMBERS

As a CMA member, you are a voting member of one of the 22 scientific specialty sections. The scientific program of each section includes a *business meeting to elect officers of the section.* These three officers—chairman, secretary, and assistant secretary—will be your representatives on the Advisory Panel to speak for you on scientific and educational issues of vital concern to your specialty: planning programs of continuing medical education; questions and controversies of acceptable medical practice; evaluation of proposed legislation, and the publication of "Epitomes of Progress" for *The Western Journal of Medicine.*

These three officers also make nominations to the Scientific Board.

Make your voice heard in these important areas by participating in the business meeting and voting for the officers of your section. See your section program for time and place.

Out of State Guests

SPECIALTY SECTION MEETINGS

Allergy

William R. Solomon, MD, Ann Arbor, Michigan
Associate Professor of Medicine, University Hospital, University of Michigan Medical Center

Anesthesiology/Physical Medicine and Rehabilitation

Richard E. Black, MD, Seattle, Washington
Assistant Professor, Department of Anesthesiology and Anesthesia Research Center, Coordinator of University Hospital Pain Clinic, University of Washington, School of Medicine

Richard C. Chapman, PhD, Seattle, Washington
Assistant Professor, Departments of Anesthesiology, Psychiatry, and Behavioral Sciences, Department of Psychology Consultant to the Pain Clinic, University of Washington, School of Medicine

Chest Diseases

Joseph F. Tomashefski, MD, Cleveland, Ohio
Head, Pulmonary Department, Cleveland Clinic; Director, Respiratory Therapy and Pulmonary Function Laboratory, Cleveland Clinic; Clinical Professor, Preventive Medicine, Ohio State University

Dermatology and Industrial Medicine

Raymond R. Suskind, MD, Cincinnati, Ohio
Director of the Department of Environmental Health and the Kettering Laboratory, University of Cincinnati

General and Family Practice/ Otolaryngology/Orthopaedics

Paul Meyer, MD, Chicago, Illinois

General Surgery

Arthur J. Donovan, MD, Mobile, Alabama
Professor and Chairman, Department of Surgery; Acting Dean, College of Medicine, University of South Alabama

Internal Medicine

Truman G. Schnabel, Jr., MD, Philadelphia, Pennsylvania
Representative, American College of Physicians

Edward C. Rosenow, Jr., MD, Philadelphia, Pennsylvania
Representative, American College of Physicians

Preventive Medicine and Public Health

Lewis C. Robbins, MD, Indianapolis, Indiana
Director, Health Hazard Appraisal, Methodist Hospital

SPECIAL CONFERENCE

Cancer Symposium

Bernard Fisher, MD, Pittsburgh, Pennsylvania
Professor of Surgery, School of Medicine, University of Pittsburgh

Ralph E. Johnson, MD, Bethesda, Maryland
Chief, Radiation Branch, National Cancer Institute

Special Conferences

FRIDAY, FEBRUARY 21

FEDERATED MEETING

Diagnostic Criteria Concerning Problems in Internal Medicine

American College of Physicians
Southern California Regions I, II and III
CMA Section on Internal Medicine

$25 Registration Fee (includes lunch on Saturday)
Advance Registration Required
Please use reservation form on Page 15

1:45 **Welcome**
Walter P. Martin, MD, Carson

1:55 **Lab Tests in Rheumatology**
Rodney Bluestone, MD, Los Angeles

2:20 **Approach to Monarticular Arthritis**
James S. Louie, MD, Torrance

2:45 **Prolapsed Mitral Leaflet Syndrome—An Important Disorder**
Michael J. Criley, MD, Torrance

3:10 Break

3:25 **Echo-cardiography—New Tool in Cardiologic Problem-Solving**
Marshall T. Morgan, MD, Los Angeles

3:50 To be announced

4:15 **Myocardial Infarction—Early Management**
Kenneth I. Shine, MD, Los Angeles

4:40 **Sexual Counseling of the Cardiac Patient**
Cynthia C. Scalzi, RN, MN, Los Angeles

5:05 Adjournment

6:00 No-host social hour

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 22

8:30 **Hepatitis**
Peter Van Doren Barrett, MD, Torrance

8:55 **Current Status of Treatment of Peptic Ulcer Diseases**
I. Michael Samloff, MD, Torrance

9:20 **G.I. Endoscopy**
Joel F. Panish, MD, Beverly Hills

9:45 **Humoral Markers of Malignant Disease**
William D. Odell, MD, Torrance

10:10 Break

10:40 **Advances in the Management of Hypertension**
Cleaves M. Bennett, MD, Torrance

11:05 **Chronic Renal Failure—1975**
Richard J. Glassock, MD, Torrance

11:30 **Presentations by Official Representatives of the American College of Physicians**
Running—What's the Good? What's the Bad?
Truman G. Schnabel, Jr., MD, Philadelphia
College Business
Edward C. Rosenow, Jr., MD, Philalelphia

12:30 **Luncheon and Panel Discussion**
Morbid Obesity
Moderator: George A. Bray, MD, Torrance
Members of the Panel
John R. Benfield, MD, Torrance
Pietro Castelnuovo-Tedesco, MD, Torrance

2:00 **Medical Complications of Oral Contraceptive Agents**
Ronald S. Swerdloff, MD, Torrance

2:25 **Current Evaluation of Thyroid Disease**
Delbert A. Fisher, MD, Torrance

2:50 **Rationale for Tight Control of the Diabetic**
Mark A. Sperling, MD, Torrance

3:15 Break

3:30 **Evaluation of the Bleeding Patient**
Herman E. Kattlove, MD, Torrance

3:55 **Logical Choice of Antimicrobial Agents**
Thomas T. Yoshikawa, MD, Torrance

4:20 **Adverse Reactions to Antibiotics**
Irwin Ziment, MD, Torrance

4:45 **Internal Medicine Section Business Meeting**

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 22

The Physician and CalOSHA

(California Occupational Safety and Health Administration)

Sponsored by
CMA Committee on Occupational Health

Moderator: Kermit H. Gruberg, MD, Berkeley

2:00 **Inspecting the Work Environment—Role of the Industrial Hygienist**
Speaker to be announced

2:45 **New Requirements for Medical Supervision—What the Doctor Must Know**
Speaker to be announced

3:30 **Exotic Occupational Health Diseases**
Speaker to be announced

4:00 **Conflicting Ethics for the Physician in Industrial Health**
Speaker to be announced

SATURDAY, FEBRUARY 22

Cancer: A Potpourri of Progress

Sponsored by
American Cancer Society, California Division

Cosponsored by
CMA Committee on Cancer

Moderator: James T. Helsper, MD, Pasadena

1:00 **Introduction**
James T. Helsper, MD, Pasadena

1:05 **Ewing's Sarcoma: A Logical Multidisciplinary Approach to the Problem**
Ralph E. Johnson, MD, Bethesda, Maryland

1:40 **What's New in Breast Cancer**
Bernard Fisher, MD, Pittsburgh, Pennsylvania

2:15 **"Smart Spheres" in the Management of Cancer: A Scientist Looks at the Problem**
William J. Dreyer, PhD, Pasadena

2:50 **Lymphoma: Improved Management and Survival Rates**
Eli J. Glatstein, MD, Stanford

3:25 **Prostatic Cancer: Results of Radiation Therapy**
Frederick W. George, III, MD, Los Angeles

4:00 **A New Diagnostic Tool for Nasopharyngeal and Laryngeal Cancers**
Paul H. Ward, MD, Los Angeles

4:35 **Oral Tumors: A New Visual Instructional Course for Physicians**
Albert M. Abrams, DDS, Los Angeles
Raymond J. Melrose, DDS, Los Angeles

4:45 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 22

Third Congress on Health of the School-Age Child

Screening for Child Health Disabilities—Issues and Answers

Cosponsored by
CMA Committee on School and College Health
California School Health Alliance

$10 Registration Fee (lunch included)
Please use reservation form on Page 23

Moderator: Robert Darter, MD, St. Helena

9:00 **Child Health Disability Prevention Program: Where Are We Now—What Are the Issues?**
Henry Shinefield, MD, San Francisco

10:15 **Screening for Child Health Disabilities—Issues and Answers**
Five Concurrent Mini-Sessions (Each Mini-Session will be repeated in the afternoon)

1. Screening vs Comprehensive Examinations
2. Developmental Tests for What?
3. Records: Why? What? Where?
4. Health Education: When? By Whom? For Whom?
5. So the Child Has a Disability—What Now? Referral, Diagnosis, Treatment

12:00 **Joint Luncheon with CMA Section on Pediatrics**
The State's Role in Health Care Policy for the 70's
Hon. Willie L. Brown, Jr., San Francisco
California State Assemblyman

Moderator: Maxine Sehring, MD, Walnut Creek

2:00 **Screening for Child Health Disabilities—Issues and Answers**
Five Concurrent Mini-Sessions (See morning session for titles)

SUNDAY, FEBRUARY 23

Alcoholism and Other Drug Dependencies: the Physician's Responsibility

Sponsored by
CMA Committee on Alcoholism and Other Drug Dependence
California Society For the Treatment of Alcoholism and Other Drug Dependencies

Cosponsored by
American Medical Society on Alcoholism, Region IX

$25 Reservation Fee (includes lunch)
Please use reservation form on Page 23

8:30 **Registration**

Moderator: Jack D. Gordon, MD, San Francisco

9:00 **Early Identification of the Alcoholic or Drug-abusing Patient**
Jude Hayes, MD, Visalia

9:30 **The Adolescent Alcoholic**
Arthur Bolter, MD, San Leandro

10:00 **The Patient Care Audit Process Applied to Alcohol-related Conditions**
Charles E. Becker, MD, San Francisco
Francis Mackey, MD, Fullerton

10:40 Break

11:00 **Update on the Treatment of Heroin Addiction**
Forest S. Tennent, Jr., MD, MPH, West Covina

11:45 **Question and Answer Period**

12:00 Luncheon

12:30 To be announced

Moderator: Arthur Bolter, MD, San Leandro

1:30 **The Sick Physician**
Max A. Schneider, MD, Orange

2:30 **Handling Pain in Patients with Substance Abuse Problems**
Barry A. Ramer, MD, San Francisco

3:10 **Question and Answer Period**

3:30 Break

3:45 **Second Annual Meeting—California Society for the Treatment of Alcoholism and Other Drug Dependencies**
Charles E. Becker, MD, President

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 23

VD Task Force Reports

JOINT MEETING

CMA Task Force on Venereal Disease
Section on Pathology

Cosponsored by

Section on Obstetrics and Gynecology
Section on Urology
Section on Dermatology
Section on General and Family Practice
Section on Pediatrics
Section on Preventive Medicine and Public Health

1:00 **Immunity in Experimental Syphilis**
James N. Miller, PhD, Los Angeles

1:20 **Serodiagnosis of Syphilis**
Eliot Wolk, MD, Downey

1:40 **Question and Answer Period**

1:50 **Genital Herpes**
Anthony W. Chow, MD, Torrance

2:10 **Trichomoniasis and Moniliasis as Venereal Diseases**
John E. Gunning, MD, Torrance

2:30 **Practical Evaluation of VD by Biopsy**
Leo Indianer, MD, Encino

2:50 **Question and Answer Period**

3:00 Break

3:20 **Is VD Education Too Tough to Handle?**
Lennin H. Glass, DrPH, Northridge

3:40 **Problems and Pitfalls in Managing the Adolescent with Venereal Disease**
Richard G. MacKenzie, MD, Los Angeles

4:00 **Screening for Asymptomatic Gonorrhea—Is it Worthwhile?**
Frank Cline, Jr., MD, Santa Barbara

4:20 **The Epidemiologist's Role in VD Control**
Mr. Sol Reiman, Downey

4:40 **Question and Answer Period**

Acceptable for Category I Credit in the CMA Certification Program

MONDAY, FEBRUARY 24

Physicians and Clergy Look at Homosexuality

Sponsored by
CMA Committee on Medicine and Religion

9:00 **Panel Discussion**
Physicians and Clergy Look at Homosexuality
Physician specializing in family practice
Psychologist
Seminarian
Minister from gay community

MONDAY, FEBRUARY 24

Current Pharmacology for the Practitioner

Sponsored by
CMA Committee on Pharmacy and Therapeutics

Cosponsored by
University of California, Irvine
California College of Medicine

9:00 **Introduction**
Moderator: Ronald Okun, MD, Los Angeles

9:15 **Newest Advances in Cancer Chemotherapy**
Charles Haskell, MD, Los Angeles

9:55 **Question and Answer Period**

10:15 **Drug Therapy of the Arthritides**
Harold Paulus, MD, Los Angeles

10:55 **Question and Answer Period**

11:15 **Rational Use of Sedative-Tranquilizers**
Henry W. Elliott, MD, Orange

11:55 **Question and Answer Period**

12:15 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

MONDAY, FEBRUARY 24

Keeping Abreast of the RVS

Sponsored by
CMA Committee on Relative Value Studies

Chairman and Moderator: Leo S. Bell, MD, San Mateo

10:00 **RVS, Current Procedural Terminology and Other Coding Systems**
Wallace A. Gerrie, Jr., MD, Newport Beach

10:15 **Philosophy of the RVS and Changes Incorporated into the 1974 Revision**
Gladden V. Elliott, MD, San Diego

10:30 **RVS and Surgical Practice**
Newlin Hastings, MD, Los Angeles

10:45 **RVS and Office Practice**
James C. Bramham, MD, Sacramento

11:00 **Question and Answer Period**

MONDAY, FEBRUARY 24

Nuclear Energy and the Public Health

Sponsored by
CMA Committee on Environmental Health

A complete program will be included in the Annual Session Handprogram

MONDAY, FEBRUARY 24

New Congress—New National Health Insurance Plans

Cosponsored by
CMA Commission on Federal Legislation
California Medical Political Action Committee

10:00 The conference will deal with the pros and cons of new national health insurance plans with regard to financing, benefit packages and administration of the plans
Speakers to be announced

12:00 Adjournment

MONDAY, FEBRUARY 24

Your Computer vs Theirs

A Conference on Data Processing for Physicians

Cosponsored by
CMA Committee on Insurance and Prepayment
Health Sciences Data Processing Society

10:00 **Introduction**
Oscar W. Hills, MD, San Mateo

10:05 **Panel Discussion**
Information requirements and the use of computer information systems in your medical practice in the era of fee profiles, National Health Insurance, PSROs, HMOs, Medicare and Medicaid
Moderator: Mr. William C. Clauer, Van Nuys
Members of the Panel to be announced

11:15 **Question and Answer Period**

MONDAY, FEBRUARY 24

Ambulatory Care Review

An Evanescent Opportunity for Medicine

Sponsored by
CMA Commission on Peer Review

Chairman: Rodrick J. Hinshaw, MD, San Bernardino

1:00 **An Opportunity for Leadership**
Thomas Elmendorf, MD, Davis

1:15 **Public Expectations: The Issue of Accountability**
Philip Lee, MD, San Francisco
Mr. George Dusheck, San Francisco
Mr. C. Bruce Sutherland, San Francisco

2:15 **Government's Response**
A California legislator experienced in state health care legislation
A member of Congress experienced in federal health care legislation
Michael Goran, MD, Washington, D.C.

3:00 Coffee Break

3:15 **The State of the Art**
Robert M. Bartel, MD, San Diego
Mr. Thomas C. Paton, San Francisco
Leonard Rubin, MD, Oakland

4:00 **Panel Discussion**
Where Do We Go From Here?
Moderator: Rodrick J. Hinshaw, MD
Thomas Elmendorf, MD, Davis
Mr. George Dusheck, San Francisco
Leonard Rubin, MD, Oakland

4:30 **Question and Answer Period**

4:45 **Conclusion**
Rodrick J. Hinshaw, MD, San Bernardino

EMERGENCY CALLS AND MESSAGES

LOS ANGELES CONVENTION CENTER
(213) 741-2193
9:00 a.m. to 5:00 p.m., Friday-Monday

BILTMORE HOTEL
(213) 629-6416
9:00 a.m. to 5:00 p.m., Saturday-Wednesday

Specialty Section Meetings

ALLERGY

Julian L. Harwell, MD, Pasadena ..... *Chairman*
William J. Sayer, MD, Palo Alto ..... *Secretary*
Arthur Turk, MD, Garden Grove ..... *Assistant Secretary*

SATURDAY, FEBRUARY 22

DINNER MEETING

Cosponsored by
Section on Chest Diseases
Stanford University School of Medicine
California Society of Allergy and Clinical Immunology

$25 Reservation Fee
By preregistration only
Please use reservation form on Page 23

Spouses and guests invited

6:00 No-host cocktails

7:00 Dinner
The Medicated or Allergic Patient and Informed Consent—Where Do We Stand?
Harold L. Engel, MD, LLB, Los Angeles

8:00 **Question and Answer Period**

SUNDAY, FEBRUARY 23

Quiz the Experts

BREAKFAST SEMINARS

Cosponsored by
Section on Chest Diseases
Stanford University School of Medicine
California Society of Allergy and Clinical Immunology

$12 Reservation Fee
By preregistration only
Please use reservation form on Page 23
Please specify seminar desired

7:30-8:30 **BREAKFAST SEMINARS** (Select One)

Each Seminar is limited to 14 persons

1. **Allergy Skin Testing and Testing for Immunologic Competence**
   Stanley P. Galant, MD, Irvine
2. **Testing for Sensitivity to Food Additives**
   Ben F. Feingold, MD, San Francisco
3. **Direct Nasal Allergic Challenge**
   William R. Solomon, MD, Ann Arbor, Michigan
4. **Laboratory Diagnosis of Hypersensitivity Pneumonitides**
   Mr. Ian D. Wells, Medical Technologist, Irvine
5. **Assessment of Airborne Mold Spores**
   William J. Sayer, MD, Palo Alto
6. **Allergy Laboratory Tests—RAST, RIST, etc.**
   Zack H. Haddad, MD, Los Angeles
7. **Food Allergy Testing**
   Douglas C. Heiner, MD, Torrance

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 23

Testing and Treatment of Respiratory Allergy

Cosponsored by
Section on Chest Diseases
Stanford University School of Medicine
California Society of Allergy and Clinical Immunology

$15 Reservation Fee
Please use reservation form on Page 23

Moderator: William J. Sayer, MD, Palo Alto

8:35 **Introduction**
Julian L. Harwell, MD, Pasadena

8:40 **Allergic and Immunologic Skin Testing**
Stanley P. Galant, MD, Irvine

9:10 **Laboratory Testing of the Allergic Patient**
Zack H. Haddad, MD, Los Angeles

9:40 **Question and Answer Period**

9:50 **Allergic Nasal Challenge**
William R. Solomon, MD, Ann Arbor, Michigan

10:35 Coffee Break

10:40 **Testing for Food Allergy**
Douglas C. Heiner, MD, Torrance

11:20 **Direct Bronchial Allergic Challenge**
Donald D. Stevenson, MD, La Jolla

11:40 **Question and Answer Period**

12:15 **Allergy Section Business Meeting and Business Meeting of California Society of Allergy and Clinical Immunology**

12:30 Luncheon
Advance Registration Only

Moderator: Arthur L. Turk, MD, Garden Grove

2:00 **Hyperkinesis and Learning Disabilities (H-LD) Linked to the Ingestion of Artificial Flavors and Colors**
Ben F. Feingold, MD, San Francisco

2:50 **Question and Answer Period**

3:00 **An Assessment of Newer Bronchodilators**
Harold S. Novey, MD, Orange

3:20 **What Chromolyn Sodium May Do for Asthmatic Patients**
Brent Burdette, MD, San Francisco

3:40 Coffee Break

3:50 **Up-To-Date Treatment of Status Asthmaticus**
William R. Solomon, MD, Ann Arbor, Michigan

4:50 **Question and Answer Period**

Acceptable for Category I Credit in the CMA Certification Program

ANESTHESIOLOGY

Edwin H. Lewis, MD, San Diego ..... *Chairman*
Lynn Winchester, MD, Palo Alto ..... *Secretary*
David Drew, MD, San Diego ..... *Assistant Secretary*

FRIDAY, FEBRUARY 21

Newer Concepts in Pain Control

JOINT MEETING
Section on Anesthesiology
Section on Physical Medicine and Rehabilitation

Cosponsored by
University of Southern California, School of Medicine

$50 Reservation Fee
(for 2-day meeting with lunch each day)
By preregistration only
Please use reservation form on Page 24

Moderator: William LaJoie, MD, Palos Verdes Peninsula

8:00 **Introduction**
Seth H. Douthett, MD, Long Beach

8:15 **Neurophysiological Basis of Pain**
Benjamin L. Crue, Jr., MD, Duarte

9:00 **Behavioral and Psychological Aspects of Pain Control**
Richard A. Sternbach, PhD, San Diego

9:45 **Question and Answer Period**

Coffee Break

10:15 **What is Pain? Analysis of the Chronic Pain Patient**
Richard G. Black, MD, Seattle

11:00 **Neurosurgical Approaches to Pain**
Attila Felsööry, MD, Duarte

11:45 **Question and Answer Period**

12:00 Luncheon

1:30 **Chronic Skeletoneuromuscular Pain with Resultant Disability**
René Cailliet, MD, Los Angeles

2:00 **Psychological Aspects of the Chronic Pain Patient**
Jack J. Pinsky, MD, Duarte

2:30 **Biofeedback Training as an Approach to the Treatment of Chronic Pain**
Melvyn R. Werbach, MD, Encino

3:00 **Question and Answer Period**

Coffee Break

3:30 **Experimental Approaches to the Use of Biofeedback in Treatment of Chronic Pain**
Roger Coger, PhD, Los Angeles

4:00 **Acupuncture for the Surgical Control of Pain in the People's Republic of China**
Richard C. Chapman, PhD, Seattle

4:45 **Question and Answer Period**

5:00 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 22

Moderator: Lynn W. Winchester, MD, Palo Alto

8:20 **Introduction**
Edwin H. Lewis, MD, San Diego

8:30 **Acupuncture in Acute and Chronic Pain Problems**
Norman Levin, MD, Northridge

9:00 **Current Research on Acupuncture Analgesia**
David E. Bresler, PhD, Westwood

9:30 **Scientific Rationale for Acupuncture Anesthesia**
William S. Kroger, MD, Beverly Hills

10:00 Coffee Break

10:15 **Japanese Ryodoraku Acupuncture**
Richard C. Chapman, PhD, Seattle

11:00 **Hypnotic Management of Pain**
William S. Kroger, MD, Beverly Hills

11:30 **Question and Answer Period**

12:00 Luncheon with Issue-Oriented Roundtable Discussions

1:30 **Operant Conditioning Program for Chronic Pain**
Seth H. Douthett, MD, Long Beach
Siebert Pearson, MD, Long Beach

2:00 **Transcutaneous Electrical Stimulation for Pain Control**
Yoshio Hosobuchi, MD, San Francisco

2:30 **Use of Nerve Blocks in Office Practice for Pain Control**
Richard G. Black, MD, Seattle

3:00 **Question and Answer Period**

Coffee Break

3:30 **Management of Pain of Central Origin**
Yoshio Hosobuchi, MD, San Francisco

4:00 **Panel Discussion**
The Pain Clinic: Selection of Patients and Organization
Moderator: Benjamin L. Crue, MD, Duarte
Members of the Panel
Richard G. Black, MD, Seattle
Verne L. Brechner, MD, Westwood
Richard A. Sternbach, PhD, San Diego

5:00 **Anesthesiology Section Business Meeting**

Acceptable for Category I Credit in the CMA Certification Program

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Plan to Visit the Exhibits

Los Angeles Convention Center

9:00 a.m. to 5:00 p.m.

FRIDAY-MONDAY

CHEST DISEASES

Robert B. Stone, MD, Oakland ..... *Chairman*
Wilbur Y. Hallett, MD, Burbank ..... *Secretary*
Hurley L. Motley, MD, Los Angeles ..... *Assistant Secretary*

SATURDAY, FEBRUARY 22

Respiratory Therapy, Basic Information and Clinical Conditions

Cosponsored by
California Chapter, American College of Chest Physicians
California Thoracic Society
Section on Allergy

Moderator: Hurley L. Motley, MD, Los Angeles

9:00 **Spirometry, Lung Volumes, Airways Resistance, Compliance, Flow Volume Loops and Airways Closing**
Joseph F. Tomashefski, MD, Cleveland

9:45 **Blood Gases and Acid-Base**
Irwin Ziment, MD, Los Angeles

10:10 Coffee Break

10:25 **Lung Scanning, Ventilation and Perfusion**
Leonard A. Swanson, MD, Los Angeles

10:55 **Alpha I-Antitrypsin**
Jack Lieberman, MD, Duarte

11:25 **National Board of Respiratory Therapy: Past, Present, and Future**
Joseph F. Tomashefski, MD, Cleveland

11:45 **Chest Diseases Section Business Meeting**

12:00 Luncheon Break

Moderator: Wilbur Y. Hallett, MD, Burbank

2:00 **Hyperbaric Oxygen Treatment for Burns**
Roman L. Yanda, MD, Van Nuys

2:30 **Aspiration Pneumonia**
Ralph C. Jung, MD, Los Angeles

3:00 **Therapy in Chronic Obstructive Pulmonary Disease**
John K. Shirey, MD, Los Angeles

3:30 Coffee Break

3:45 **Respiratory Distress Syndrome**
Joseph F. Tomashefski, MD, Cleveland

4:30 **Panel Discussion**
Doctors Hallett, Jung, Shirey, Tomashefski, and Yanda

5:00 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

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Plan to Visit the Exhibits

Los Angeles Convention Center

9:00 a.m. to 5:00 p.m.

FRIDAY-MONDAY

DERMATOLOGY

Ellis N. Mitchell, MD, Greenbrae ..... *Chairman*
Marian M. Brubaker, MD, La Canada ..... *Secretary*
Faye D. Arundell, MD, Stanford ..... *Assistant Secretary*

SATURDAY, FEBRUARY 22

Clinical Meeting

Los Angeles County-USC Medical Center
(Women's Hospital)
1200 North State Street
Los Angeles

Cosponsored by
University of Southern California School of Medicine, Dermatology Section
Los Angeles Dermatological Society
Metropolitan Dermatological Society of Los Angeles

1:30 **Clinical Meeting and Case Presentations**

2:30 **Discussion of Clinical Cases**

4:00 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

DINNER

The Los Angeles Music Center
Eldorado Room
135 N. Grand Avenue, Los Angeles

$14 Advance Registration Required
Deadline February 15, 1975
Please use reservation form on Page 23
Members and guests invited

6:30 Cocktail hour

7:30 Dinner

SUNDAY, FEBRUARY 23

Occupational Dermatoses

JOINT MEETING
Section on Dermatology
Section on Industrial Medicine and Surgery

Cosponsored by
University of Southern California School of Medicine Dermatology Section

Moderator: Ellis N. Mitchell, MD, Greenbrae

8:45 **Dermatology Section Business Meeting**

9:00 **Occupational Skin Diseases in California—Extent of the Problem**
Robert M. Adams, MD, Palo Alto

9:20 **Cutaneous Manifestations of Trichloroethylene Toxicity**
Marjorie F. Bauer, MD, Los Angeles

9:40 **Environmental Aspects of Occupational Skin Disease**
Raymond R. Suskind, MD, Cincinnati

10:20 **Question and Answer Period**

10:35 Coffee Break

Moderator: Walter J. Gillogley, MD, Sunnyvale

10:50 **Panel Discussion**
Worker's Compensation Problems in the Management of Industrial Dermatoses

Moderator: Edward J. O'Neill, MD, Woodland Hills

Members of the Panel
Norman E. Levan, MD, Los Angeles
Robert M. Adams, MD, Palo Alto
Raymond R. Suskind, MD, Cincinnati
Milton J. Litvin, Esq., Los Angeles
Jerome A. Berman, Esq., Los Angeles

12:00 **Question and Answer Period**

Acceptable for Category I Credit In the CMA Certification Program

GENERAL AND FAMILY PRACTICE

Ransom B. Turner, MD, Santa Rosa ..... *Chairman*
Caesar O. Julian, MD, Simi Valley ..... *Secretary*
John F. Bridgeman, MD, Mission Viejo .. *Assistant Secretary*

SATURDAY, FEBRUARY 22

Emergency and Immediate Care of Head and Neck Injuries

JOINT MEETING
Section on General and Family Practice
Section on Orthopaedics
Section on Otolaryngology

Cosponsored by
University of California, Irvine
California College of Medicine

1:00 **Introduction**
Robert I. Kohut, MD, Irvine

1:05 **Emergency Room Problems of the Head and Neck: The Physician Who Sees Them First**
William Nesbitt, MD, Davis

1:20 **Panel Discussion**
Life Threatening Problems

Moderator: Steven Pye, MD, San Diego

Airway
Alden Miller, MD, Los Angeles
Bleeding
William Simpson, MD, Los Angeles
Middle Meningeal (Cerebral)
Eldon Foltz, MD, Irvine
John Kusske, MD, Irvine
Cervical Spine
Paul Meyer, MD, Chicago

2:20 Coffee Break

2:40 **Panel Discussion**
Complications and Consequences of Initial Care and Timetable

Moderator: Steven Pye, MD, San Diego

3:00 **Recognition and Initial Treatment of Emergency Eye Injuries**
George Tabor, MD, San Diego

4:15 **Delivery of Multidisciplinary Medical Care in Acute Injury (Spinal Cord)**
Paul Meyer, MD, Chicago

5:00 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 23

Moderator:
Simon C. Brumbaugh, Jr., MD, Lemon Grove

9:00 **Facial Fractures**
Alan Nahum, MD, San Diego
James Anhalt, MD, Irvine

9:30 **Nasal Injuries**
Paul J. Donald, MD, Davis
John F. Bridgeman, MD, Mission Viejo

10:00 **Dental Problems**
Frank S. Drongowski, DDS, Lemon Grove
Rio Yamamoto, MD, Garden Grove

10:30 Coffee Break

10:50 **Airway Injuries**
Rinaldo Canalis, MD, Torrance
Roger A. Forsyth, MD, Los Angeles

11:20 **Soft Tissue Injuries and Care of the Facial Nerve**
Roger Boles, MD, San Francisco
Wesley H. Geer, MD, Fullerton

11:50 **Burns of the Head and Neck**
Robert Bartlett, MD, Irvine
John P. Crivaro, MD, Long Beach

12:20 Lunch Break

1:30 **General and Family Practice Section Business Meeting**

2:00 **Ear Trauma**
Willard Fee, MD, Palo Alto
Marc Richmond, MD, Irvine

2:20 **Cervical Spine Injuries**
Paul Meyer, MD, Chicago
J. Blair Pace, MD, Irvine

2:40 **Intracranial Injuries**
Eldon Foltz, MD, Irvine
John Kusske, MD, Irvine
Raymond C. Anderson, MD, Irvine

3:30 Coffee Break

3:45 **Problem Cases of Various Types**
Moderator:
Simon C. Brumbaugh, Jr., MD, Lemon Grove

5:00 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

GENERAL SURGERY

David B. Hinshaw, MD, Loma Linda ..... *Chairman*
Earl F. Wolfman, Jr., MD, Davis ..... *Secretary*
Fred L. Turrill, MD, Glendale ..... *Assistant Secretary*

FRIDAY, FEBRUARY 21

Cosponsored by
American College of Surgeons
Northern California, Southern California, and San Diego Chapters

$10 Registration Fee
Please use reservation form on Page 24

Moderator: David B. Hinshaw, MD, Loma Linda

12:00 **Luncheon Meeting** with American College of Surgeons, Northern California, Southern California, and San Diego Chapters

12:45 **Luncheon Address: Causes of Death from Trauma and Surgery**
Arthur J. Donovan, MD, Mobile, Alabama

Breast Surgery

1:30 **Mammography and the Surgeon**
Joseph F. Linsman, MD, Beverly Hills

1:50 **Breast Reconstruction Following Radical and Subcutaneous Mastectomies**
Eugene W. Worton, MD, Los Angeles

2:10 **Palliative Treatment of Recurrent Breast Cancer**
Arthur J. Donovan, MD, Mobile

2:30 **Panel Discussion**
Current Trends in the Diagnosis and Management of Breast Cancer

Moderator: Lewis W. Guiss, MD, Los Angeles

Members of the Panel
Arthur J. Donovan, MD, Mobile
Joseph F. Linsman, MD, Beverly Hills
Eugene W. Worton, MD, Los Angeles

3:00 Break

Liver and Biliary Tract Surgery

3:15 **The Natural History of Gallstone Disease**
Lawrence W. Way, MD, San Francisco

3:30 **Acute Biliary Tract Disease**
Ralph J. Thompson, MD, Loma Linda

3:45 **Postoperative Jaundice: Approach to a Diagnostic Dilemma**
Leon Morgenstern, MD, Los Angeles

4:00 **The Clinical Significance of Gas in the Portal Vein in Intestinal Ischemia**
Thomas V. Berne, MD, Los Angeles

4:15 **Hepatic Trauma**
Arthur J. Donovan, MD, Mobile

4:45 **General Surgery Section Business Meeting**

Acceptable for Category I Credit in the CMA Certification Program

INDUSTRIAL MEDICINE AND SURGERY

John Meyers, MD, San Francisco ..... *Chairman*
Edward J. O'Neill, MD, Woodland Hills ..... *Secretary*
Austin E. Givens, MD, Danville ..... *Assistant Secretary*

SUNDAY, FEBRUARY 23

Occupational Dermatoses

JOINT MEETING
Section on Industrial Medicine and Surgery
Section on Dermatology

Cosponsored by
University of Southern California School of Medicine Dermatology Section

Moderator: Ellis N. Mitchell, MD, Greenbrae

9:00 **Occupational Skin Diseases in California—Extent of the Problem**
Robert M. Adams, MD, Palo Alto

9:20 **Cutaneous Manifestations of Trichloroethylene Toxicity**
Marjorie F. Bauer, MD, Los Angeles

9:40 **Environmental Aspects of Occupational Skin Disease**
Raymond R. Suskind, MD, Cincinnati

10:20 **Question and Answer Period**

10:35 Coffee Break

Moderator: Walter J. Gillogley, MD, Sunnyvale

10:50 **Panel Discussion**
Worker's Compensation Problems in the Management of Industrial Dermatoses

Moderator: Edward J. O'Neill, MD, Woodland Hills

Members of the Panel
Norman E. Levan, MD, Los Angeles
Robert M. Adams, MD, Palo Alto
Raymond R. Suskind, MD, Cincinnati
Milton J. Litvin, Esq., Los Angeles
Jerome A. Berman, Esq., Los Angeles

12:00 **Question and Answer Period**

12:15 **Industrial Medicine and Surgery Section Business Meeting**

Acceptable for Category I Credit in the CMA Certification Program

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EMERGENCY CALLS AND MESSAGES

LOS ANGELES CONVENTION CENTER
(213) 741-2193
9:00 a.m. to 5:00 p.m., Friday-Monday

BILTMORE HOTEL
(213) 629-6416
9:00 a.m. to 5:00 p.m., Saturday-Wednesday

INTERNAL MEDICINE

Edwin V. Banta, MD, Redlands ..... *Chairman*
Daniel W. Black, MD, Castro Valley ..... *Secretary*

FRIDAY, FEBRUARY 21

FEDERATED MEETING

Diagnostic Criteria Concerning Problems in Internal Medicine

CMA Section on Internal Medicine
American College of Physicians
Southern California Regions I, II and III

$25 Registration Fee
Advance Registration Required
Please use reservation form below

1:45 **Welcome**
Walter P. Martin, MD, Carson

1:55 **Lab Tests in Rheumatology**
Rodney Bluestone, MD, Los Angeles

2:20 **Approach to Monarticular Arthritis**
James S. Louie, MD, Torrance

2:45 **Prolapsed Mitral Leaflet Syndrome—An Important Disorder**
Michael J. Criley, MD, Torrance

3:10 Break

3:25 **Echo-cardiography—New Tool in Cardiologic Problem-Solving**
Marshall T. Morgan, MD, Los Angeles

3:50 To be announced

4:15 **Myocardial Infarction—Early Management**
Kenneth I. Shine, MD, Los Angeles

4:40 **Sexual Counseling of the Cardiac Patient**
Cynthia C. Scalzi, RN, MN, Los Angeles

5:05 Adjournment

6:00 No-host social hour

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 22

8:30 **Hepatitis**
Peter Van Doren Barrett, MD, Torrance

8:55 **Current Status of Treatment of Peptic Ulcer Diseases**
I. Michael Samloff, MD, Torrance

9:20 **G.I. Endoscopy**
Joel F. Panish, MD, Beverly Hills

9:45 **Humoral Markers of Malignant Disease**
William D. Odell, MD, Torrance

10:10 Break

10:40 **Advances in the Management of Hypertension**
Cleaves M. Bennett, MD, Torrance

11:05 **Chronic Renal Failure—1975**
Richard J. Glassock, MD, Torrance

11:30 **Presentations by Official Representatives of the American College of Physicians**
Running—What's the Good? What's the Bad?
Truman G. Schnabel, Jr., MD, Philadelphia
College Business
Edward C. Rosenow, Jr., MD, Philadelphia

12:30 **Luncheon and Panel Discussion: Morbid Obesity**

Moderator: George A. Bray, MD, Torrance

Members of the Panel
John R. Benfield, MD, Torrance
Pietro Castelnuovo-Tedesco, MD, Torrance

2:00 **Medical Complications of Oral Contraceptive Agents**
Ronald S. Swerdloff, MD, Torrance

2:25 **Current Evaluation of Thyroid Disease**
Delbert A. Fisher, MD, Torrance

2:50 **Rationale for Tight Control of the Diabetic**
Mark A. Sperling, MD, Torrance

3:15 Break

3:30 **Evaluation of the Bleeding Patient**
Herman E. Kattlove, MD, Torrance

3:55 **Logical Choice of Antimicrobial Agents**
Thomas T. Yoshikawa, MD, Torrance

4:20 **Adverse Reactions to Antibiotics**
Irwin Ziment, MD, Torrance

4:45 **Internal Medicine Section Business Meeting**

Acceptable for Category I Credit in the CMA Certification Program

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Internal Medicine Section/American College of Physicians

Conference and Luncheon reservation

FRIDAY, FEBRUARY 21, 1:45 pm
SATURDAY, FEBRUARY 22, 8:30 am
$25

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

Please make check payable to: American College of Physicians

Return this application with total remittance to:
WALTER P. MARTIN, MD
21510 South Main Street
Carson, CA 90745

NEUROLOGY

Edward Shev, MD, San Francisco ..... *Chairman*
James R. Nelson, MD, La Jolla ..... *Secretary*
Pierre Dreyfus, MD, Davis ..... *Assistant Secretary*

SUNDAY, FEBRUARY 23

Recent Advances in Neuroradiology
Special Focus: The EMI Computerized Brain Scan

JOINT MEETING
Section on Neurology
Section on Radiology

Cosponsored by
Los Angeles County/USC Medical Center

8:45 **Neurology Section Business Meeting**

9:00 **EMI Scanner: Basic Techniques, Anatomy, Indications and Accuracy**
David F. Reese, MD, Rochester, Minnesota

9:40 **Question and Answer Period**

10:00 **EMI Scanner: Case Presentations**
David F. Reese, MD, Rochester

10:40 Coffee Break

11:00 **Cerebral Embolization—A Common Clinical Entity Not Commonly Recognized**
Calvin Rumbaugh, MD, Los Angeles

11:45 **Interventional Neuroradiology**
John R. Bentson, MD, Los Angeles

12:30 **Question and Answer Period**

Acceptable for Category I Credit in the CMA Certification Program

NUCLEAR MEDICINE

John R. White, MD, Torrance ..... *Chairman*
J. David Bernard, MD, Stockton ..... *Secretary*
Jorge Franco, MD, San Jose ..... *Assistant Secretary*

MONDAY, FEBRUARY 24

The Contribution of Nuclear Medicine to the Management of the Patient

8:30 **Nuclear Medicine Section Business Meeting**

Moderator: Joseph Ross, MD, Los Angeles

9:00 **Nuclear Medicine—State of the Art**
William Blahd, MD, Los Angeles

9:30 **Questions Bone Scans Answer**
Malcolm Powell, MD, San Francisco

10:00 **Radionuclide Brain Scanning and Cerebral Perfusion Studies**
Milo Webber, MD, Los Angeles

10:30 Break

10:45 **Hepatic and Pulmonary Nuclear Imaging**
William Ashburn, MD, San Diego

11:15 **Panel Discussion**
Doctors Ross, Blahd, Powell, Webber, Ashburn

12:00 Adjournment

OBSTETRICS AND GYNECOLOGY

Charles E. Weber, MD, La Jolla ..... *Chairman*
Theodore W. Loring, MD, Eureka ..... *Secretary*
John Molitor, MD, Fullerton ..... *Assistant Secretary*

MONDAY, FEBRUARY 24

JOINT MEETING
Section on Obstetrics and Gynecology
Section on Urology

Cosponsored by
University of California, Irvine
California College of Medicine
California Section, American College of Obstetricians and Gynecologists

$10 Reservation Fee (Includes Lunch)
Please use reservation form on Page 24

8:45 **Welcome**
Charles E. Weber, MD, La Jolla
J. Bernard Miller, MD, Santa Ana

9:00 **Management of the Critically Ill Obstetrical-Gynecology or Genitourinary Patient**
Robert Baker, MD, Chicago

10:30 Coffee Break

10:45 **Genitourinary Intensive Care Unit of Los Angeles County/USC Medical Center**
Malcolm D. Cosgrove, MD, Los Angeles

11:45 **Obstetrics and Gynecology Section Business Meeting**

12:15 Luncheon

Medical Legal Problems of Obstetricians and Urologists
David Rubsamen, MD, LLB, Berkeley

2:15 **Repair of Vesicovaginal Fistula—O/G Approach**
Speaker to be announced

2:45 **Repair of Vesicovaginal Fistula—G/U Approach**
Carl K. Pearlman, MD, Santa Ana

3:15 Coffee Break

3:30 **Female Sterilization**
Speaker to be announced

4:00 **Male Sterilization**
Stanwood S. Schmidt, MD, Eureka

Acceptable for Category I Credit in the CMA Certification Program

OPHTHALMOLOGY

Robert E. Christensen, MD, Los Angeles ..... *Chairman*
Jerry Donin, MD, Pomona ..... *Secretary*
Gilbert Cleasby, MD, San Francisco .... *Assistant Secretary*

SUNDAY, FEBRUARY 23

Symposium on Ocular Trauma

Cosponsored by
Division of Ophthalmology, Department of Surgery
University of California, San Diego

$15 Registration Fee
By Preregistration Only
Please use reservation form on Page 24

Moderator: Jerry F. Donin, MD, Pomona

9:00 **Introduction**
Robert E. Christensen, MD, Los Angeles

9:05 **Blowout Fractures**
Robert V. Shearer, MD, Loma Linda

9:20 **Eyelid Injuries**
J. Earl Rathbun, MD, Santa Rosa

9:40 **Traumatic Strabismus**
Alan B. Scott, MD, San Francisco

10:00 Coffee Break

10:20 **Intraocular Foreign Bodies**
A. Ralph Rosenthal, MD, Palo Alto

10:50 **Hysteria and Malingering Following Ocular Trauma**
George L. Tabor, MD, San Diego

11:20 **Question and Answer Period**

11:45 **Ophthalmology Section Business Meeting**

12:00 Luncheon

Members of the Executive Committee of the California Association of Ophthalmology will present brief reports on important pending legislative matters.

Moderator: George L. Tabor, MD, San Diego

1:30 **Corneal Repair in Ocular Trauma**
Robert G. Webster, Jr., MD, San Francisco

1:45 **Vitrectomy in Ocular Trauma**
Stephen J. Ryan, MD, Los Angeles

2:05 **Management of Traumatic Hyphema**
David M. Worthen, MD, San Diego

2:35 **Retinal Trauma**
Allen E. Kreiger, MD, Los Angeles

2:55 Coffee Break

3:15 **Pathologic Aspects of Ocular Trauma**
Robert E. Levine, MD, Los Angeles

3:35 **Ultrasound in the Management of Ocular Trauma**
Robert Penner, MD, Chula Vista

3:50 **Question and Answer Period**

Acceptable for Category I Credit in the CMA Certification Program

ORTHOPAEDICS

Steven Pye, MD, San Diego ..... *Chairman*
Sonny Cobble, MD, Los Angeles ..... *Secretary*

SATURDAY, FEBRUARY 22

Emergency and Immediate Care of Head and Neck Injuries

JOINT MEETING
Section on Orthopaedics
Section on General and Family Practice
Section on Otolaryngology

Cosponsored by
University of California, Irvine
California College of Medicine

1:00 **Introduction**
Robert I. Kohut, MD, Irvine

1:05 **Emergency Room Problems of the Head and Neck: The Physician Who Sees Them First**
William Nesbitt, MD, Davis

1:20 **Panel Discussion**
Life Threatening Problems

Moderator: Steven Pye, MD, San Diego

Airway
Alden Miller, MD, Los Angeles
Bleeding
William Simpson, MD, Los Angeles
Middle Meningeal (Cerebral)
Eldon Foltz, MD, Irvine
John Kusske, MD, Irvine
Cervical Spine
Paul Meyer, MD, Chicago

2:20 Coffee Break

2:40 **Panel Discussion**
Complications and Consequences of Initial Care and Timetable

Moderator: Steven Pye, MD, San Diego

3:00 **Recognition and Initial Treatment of Emergency Eye Injuries**
George Tabor, MD, San Diego

4:15 **Delivery of Multidisciplinary Medical Care in Acute Injury (Spinal Cord)**
Paul Meyer, MD, Chicago

5:00 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 23

Moderator:
Simon C. Brumbaugh, Jr., MD, Lemon Grove

9:00 **Facial Fractures**
Alan Nahum, MD, San Diego
James Anhalt, MD, Irvine

9:30 **Nasal Injuries**
Paul J. Donald, MD, Davis
John F. Bridgeman, MD, Mission Viejo

10:00 **Dental Problems**
Frank S. Drongowski, DDS, Lemon Grove
Rio Yamamoto, MD, Garden Grove

10:30 Coffee Break

10:50 **Airway Injuries**
Rinaldo Canalis, MD, Torrance
Roger A. Forsyth, MD, Los Angeles

11:20 **Soft Tissue Injuries and Care of the Facial Nerve**
Roger Boles, MD, San Francisco
Wesley H. Geer, MD, Fullerton

11:50 **Burns of the Head and Neck**
Robert Bartlett, MD, Irvine
John P. Crivaro, MD, Long Beach

12:20 Lunch Break

1:30 **Orthopaedics Section Business Meeting**

2:00 **Ear Trauma**
Willard Fee, MD, Palo Alto
Marc Richmond, MD, Irvine

2:20 **Cervical Spine Injuries**
Paul Meyer, MD, Chicago
J. Blair Pace, MD, Irvine

2:40 **Intracranial Injuries**
Eldon Foltz, MD, Irvine
John Kusske, MD, Irvine
Raymond C. Anderson, MD, Irvine

3:30 Coffee Break

3:45 **Problem Cases of Various Types**
Moderator:
Simon C. Brumbaugh, Jr., MD, Lemon Grove

5:00 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

OTOLARYNGOLOGY

William Simpson, MD, Los Angeles ..... *Chairman*
Mansfield Smith, MD, Stanford ..... *Secretary*
Robert I. Kohut, MD, Irvine ..... *Assistant Secretary*

SATURDAY, FEBRUARY 22

Emergency and Immediate Care of Head and Neck Injuries

JOINT MEETING
Section on Otolaryngology
Section on General and Family Practice
Section on Orthopaedics

Cosponsored by
University of California, Irvine
California College of Medicine

1:00 **Introduction**
Robert I. Kohut, MD, Irvine

1:05 **Emergency Room Problems of the Head and Neck: The Physician Who Sees Them First**
William Nesbitt, MD, Davis

1:20 **Panel Discussion**
Life Threatening Problems

Moderator: Steven Pye, MD, San Diego

Airway
Alden Miller, MD, Los Angeles
Bleeding
William Simpson, MD, Los Angeles
Middle Meningeal (Cerebral)
Eldon Foltz, MD, Irvine
John Kusske, MD, Irvine
Cervical Spine
Paul Meyer, MD, Chicago

2:20 Coffee Break

2:40 **Panel Discussion**
Complications and Consequences of Initial Care and Timetable

Moderator: Steven Pye, MD, San Diego

3:00 **Recognition and Initial Treatment of Emergency Eye Injuries**
George Tabor, MD, San Diego

4:15 **Delivery of Multidisciplinary Medical Care in Acute Injury (Spinal Cord)**
Paul Meyer, MD, Chicago

5:00 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 23

Moderator:
Simon C. Brumbaugh, Jr., MD, Lemon Grove

9:00 **Facial Fractures**
Alan Nahum, MD, San Diego
James Anhalt, MD, Irvine

9:30 **Nasal Injuries**
Paul J. Donald, MD, Davis
John F. Bridgeman, MD, Mission Viejo

10:00 **Dental Problems**
Frank S. Drongowski, DDS, Lemon Grove
Rio Yamamoto, MD, Garden Grove

10:30 Coffee Break

10:50 **Airway Injuries**
Rinaldo Canalis, MD, Torrance
Roger A. Forsyth, MD, Los Angeles

11:20 **Soft Tissue Injuries and Care of the Facial Nerve**
Roger Boles, MD, San Francisco
Wesley H. Geer, MD, Fullerton

11:50 **Burns of the Head and Neck**
Robert Bartlett, MD, Irvine
John P. Crivaro, MD, Long Beach

12:20 Lunch Break

1:30 **Otolaryngology Section Business Meeting**

2:00 **Ear Trauma**
Willard Fee, MD, Palo Alto
Marc Richmond, MD, Irvine

2:20 **Cervical Spine Injuries**
Paul Meyer, MD, Chicago
J. Blair Pace, MD, Irvine

2:40 **Intracranial Injuries**
Eldon Foltz, MD, Irvine
John Kusske, MD, Irvine
Raymond C. Anderson, MD, Irvine

3:30 Coffee Break

3:45 **Problem Cases of Various Types**
Moderator:
Simon C. Brumbaugh, Jr., MD, Lemon Grove

5:00 Adjournment

Acceptable for Category I Credit In the CMA Certification Program

PATHOLOGY

Phillips L. Gausewitz, MD, La Jolla ..... *Chairman*
Stebbins Chandor, MD, Los Angeles ..... *Secretary*
Joseph H. Masters, MD, Sacramento ... *Assistant Secretary*

VD Task Force Reports

JOINT MEETING
Section on Pathology
CMA Task Force on Venereal Disease

Cosponsored by
Section on Obstetrics and Gynecology
Section on Urology
Section on Dermatology
Section on General and Family Practice
Section on Pediatrics
Section on Preventive Medicine and Public Health

SUNDAY, FEBRUARY 23

1:00 **Immunity in Experimental Syphilis**
James N. Miller, PhD, Los Angeles

1:20 **Serodiagnosis of Syphilis**
Eliot Wolk, MD, Downey

1:40 **Question and Answer Period**

1:50 **Genital Herpes**
Anthony W. Chow, MD, Torrance

2:10 **Trichomoniasis and Moniliasis as Venereal Diseases**
John E. Gunning, MD, Torrance

2:30 **Practical Evaluation of VD by Biopsy**
Leo Indianer, MD, Encino

2:50 **Question and Answer Period**

3:00 Break

3:20 **Is VD Education Too Tough to Handle?**
Lennin H. Glass, DrPH, Northridge

3:40 **Problems and Pitfalls in Managing the Adolescent with Venereal Disease**
Richard G. MacKenzie, MD, Los Angeles

4:00 **Screening for Asymptomatic Gonorrhea—Is It Worthwhile?**
Frank Cline, Jr., MD, Santa Barbara

4:20 **The Epidemiologist's Role in VD Control**
Mr. Sol Reiman, Downey

4:40 **Question and Answer Period**

Acceptable for Category I Credit in the CMA Certification Program

PEDIATRICS

Lee P. Smith, MD, Mill Valley ..... *Chairman*
Nord S. Nation, MD, Los Angeles ..... *Secretary*
Edward J. Ottenheimer, MD, San Diego ..*Assistant Secretary*

SATURDAY, FEBRUARY 22

Cosponsored by
American Academy of Pediatrics

$10 Reservation Fee
By preregistration only
Please use reservation form on Page 24

Chairman: Nord S. Nation, MD, Los Angeles

8:45 **Introduction**

Moderator: Lee P. Smith, MD, Mill Valley

9:00 **Pitfalls and Pratfalls in Pediatric Radiology**
Isaac Sanders, MD, Los Angeles

9:40 **Sleep Disorders in Childhood**
Bruce O. Berg, MD, San Francisco

10:20 Coffee Break

10:40 **The Responsibility of Adolescents to Parents**
Martin Gershman, MD, San Francisco

11:20 **Exotic Parasitic Diseases in California**
Allen W. Mathies, Jr., MD, Los Angeles

12:00 **Question and Answer Period**

12:30 Luncheon
The State's Role in Health Care Policy for the 70's
Hon. Willie L. Brown, Jr., San Francisco
California State Assemblyman

Chairman: William D. Misbach, MD, Encino

2:00 **Control of Nosocomial Infections Among Pediatric Patients**
Paul F. Wehrle, MD, Los Angeles

2:40 **Pediatric Emergencies—The Changing Scene**
Delmer J. Pascoe, MD, San Francisco

3:20 **The Pediatrician's Misuse of Drugs**
Robert H. Levin, PhD, San Francisco

4:00 **The Everyday Problems in Managing Juvenile Diabetes Mellitus**
Neil N. Litman, MD, Los Angeles

4:40 **Question and Answer Period**

5:00 **Pediatrics Section Business Meeting**

Acceptable for Category I Credit In the CMA Certification Program

PHYSICAL MEDICINE AND REHABILITATION

Seth Douthett, MD, Long Beach ..... *Chairman*
Walter Treanor, MD, San Francisco ..... *Secretary*
William LaJoie, MD,
Palos Verdes Peninsula ..... *Assistant Secretary*

FRIDAY, FEBRUARY 21

Newer Concepts in Pain Control

JOINT MEETING
Section on Physicial Medicine and Rehabilitation
Section on Anesthesiology

Cosponsored by
University of Southern California, School of Medicine

$50 Reservation Fee
(for 2-day meeting with lunch each day)
By preregistration only
Please use reservation form on Page 24

Moderator:
William LaJoie, MD, Palos Verdes Peninsula

8:00 **Introduction**
Seth H. Douthett, MD, Long Beach

8:15 **Neurophysiological Basis of Pain**
Benjamin L. Crue, Jr., MD, Duarte

9:00 **Behavioral and Psychological Aspects of Pain Control**
Richard A. Sternbach, PhD, San Diego

9:45 **Question and Answer Period**

Coffee Break

10:15 **What is Pain? Analysis of the Chronic Paln Patient**
Richard G. Black, MD, Seattle

11:00 **Neurosurgical Approaches to Pain**
Attila Felsööry, MD, Duarte

11:45 **Question and Answer Period**

12:00 Luncheon

1:30 **Chronic Skeletoneuromuscular Pain with Resultant Disability**
René Cailliet, MD, Los Angeles

2:00 **Psychological Aspects of the Chronic Pain Patient**
Jack J. Pinsky, MD, Duarte

2:30 **Biofeedback Training as an Approach to the Treatment of Chronic Pain**
Melvyn R. Werbach, MD, Encino

3:00 **Question and Answer Period**

Coffee Break

3:30 **Experimental Approaches to the Use of Biofeedback in Treatment of Chronic Pain**
Roger Coger, PhD, Los Angeles

4:00 **Acupuncture for the Surgical Control of Pain in the People's Republic of China**
Richard C. Chapman, PhD, Seattle

4:45 **Question and Answer Period**

5:00 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 22

Moderator: Lynn W. Winchester, MD, Palo Alto

8:20 **Introduction**
Edwin H. Lewis, MD, San Diego

8:30 **Acupuncture in Acute and Chronic Pain Problems**
Norman Levin, MD, Northridge

9:00 **Current Research on Acupuncture Analgesia**
David E. Bresler, PhD, Westwood

9:30 **Scientific Rationale for Acupuncture Anesthesia**
William S. Kroger, MD, Beverly Hills

10:00 Coffee Break

10:15 **Japanese Ryodoraku Acupuncture**
Richard C. Chapman, PhD, Seattle

11:00 **Hypnotic Management of Pain**
William S. Kroger, MD, Beverly Hills

11:30 **Question and Answer Period**

12:00 Luncheon with Issue-Oriented Roundtable Discussions

1:30 **Operant Conditioning Program for Chronic Pain**
Seth H. Douthett, MD, Long Beach
Siebert Pearson, MD, Long Beach

2:00 **Transcutaneous Electrical Stimulation for Pain Control**
Yoshio Hosobuchi, MD, San Francisco

2:30 **Use of Nerve Blocks in Office Practice for Pain Control**
Richard G. Black, MD, Seattle

3:00 **Question and Answer Period**

Coffee Break

3:15 **Physical Medicine and Rehabilitation Section Business Meeting**

3:30 **Management of Pain of Central Origin**
Yoshio Hosobuchi, MD, San Francisco

4:00 **Panel Discussion**
The Pain Clinic: Selection of Patients and Organization

Moderator: Benjamin L. Crue, MD, Duarte

Members of the Panel
Richard G. Black, MD, Seattle
Verne L. Brechner, MD, Westwood
Richard A. Sternbach, PhD, San Diego

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EMERGENCY CALLS AND MESSAGES

LOS ANGELES CONVENTION CENTER
(213) 741-2193
9:00 a.m. to 5:00 p.m., Friday-Monday

BILTMORE HOTEL
(213) 629-6416
9:00 a.m. to 5:00 p.m., Saturday-Wednesday

PLASTIC SURGERY

Roger P. Friedenthal, MD, San Francisco ..... *Chairman*
Frederick M. Grazer, MD, Newport Beach ..... *Secretary*
Richard Dakin, MD, Greenbrae ..... *Assistant Secretary*

MONDAY, FEBRUARY 24

Principles of Plastic Surgical Wound Closure

Cosponsored by
Schools of Medicine: Irvine, Loma Linda, UCLA, USC
California Society of Plastic Surgeons

$25 Registration fee for Laboratory

Please use reservation form on Page 24

Laboratory limited to 50 participants

LABORATORY

8:30 **Practical Applications of Z-Plasty and Related Small Flap Techniques.** Biological specimens and equipment supplied.

Members of the Faculty
Gary S. Brody, MD, Los Angeles
Hugh H. Crawford, MD, Irvine
David W. Furnas, MD, Irvine
Harvey L. Heinrichs, MD, Irvine
Lawrence Seifert, MD, Los Angeles
John O. Strong, MD, Irvine
Eugene W. Worton, MD, Los Angeles
Harvey A. Zaren, MD, Los Angeles

Open Session

0:30 **Practical Applications of Wound Closure Covered in Laboratory**
David W. Furnas, MD, Irvine

1:15 **Recent Advances in Burn Therapy**
Lawrence Seifert, MD, Los Angeles

1:00 **Physical Diagnosis of the Acutely Injured Hand**
Gary S. Brody, MD, Los Angeles

1:45 **Treatment of the Acutely Injured Hand—What is the Proper Emergency Room Treatment?**
Hugh H. Crawford, MD, Irvine

2:30 **What's New in Pressure Sore Therapy?**
Libby F. Wilson, MD, Los Angeles

3:00 Coffee Break

3:15 **Treatment of the Unacceptable Scar—What is a Keloid?**
Thomas J. Zirkle, MD, Loma Linda

3:45 **What's New in Plastic Surgery—What Makes a Good Plastic Surgical Patient?**
Harvey A. Zarem, MD, Los Angeles

4:45 **Plastic Surgery Section Business Meeting**

Acceptable for Category I Credit in the CMA Certification Program

PREVENTIVE MEDICINE AND PUBLIC HEALTH

Colin T. Greenlaw, MD, Sacramento ..... *Chairman*
Allyn G. Bridge, MD, Riverside ..... *Secretary*
Stephan Billstein, MD, Sacramento .... *Assistant Secretary*

SATURDAY, FEBRUARY 22

Clinical Preventive Medicine

Health Promotion, Disease Anticipation, and Prevention of Chronic Disease

Cosponsored by
University of California, Los Angeles
School of Public Health

Moderator: Allyn G. Bridge, MD, Riverside

9:00 **Prevention in Medical Practice**
Gary D. Friedman, MD, Oakland

9:30 **Family Practice and Preventive Medicine, A New Synergism**
Lewis C. Robbins, MD, Indianapolis

10:30 Coffee Break

10:45 **Risk Appraisal in Private Practice**
Robert J. Werra, MD, Ukiah

11:15 **Reaction and Comments**
Lester Breslow, MD, Los Angeles

11:25 **Question and Answer Period**

Moderator: Colin T. Greenlaw, MD, Sacramento

1:15 **Prevention of Cancer of the Breast and Cervix**
Elfriede Fasal, MD, Sacramento

1:35 **Prevention of Chronic Urinary Infections and Their Consequences**
Lauri D. Thrupp, MD, Orange

1:55 **Prevention of Dental Disease**
Daniel J. Corrigan, DDS, Sacramento

2:15 Coffee Break

2:35 **Prevention of Lung Diseases**
Stanley N. Rokaw, MD, Lynwood

2:55 **Prevention of Hypertension and Related Problems**
Ellin Lieberman, MD, Los Angeles

3:15 **Question and Answer Period**

3:30 **Preventive Medicine and Public Health Section Business Meeting**

Acceptable for Category I Credit in the CMA Certification Program

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Plan to Visit the Exhibits

Los Angeles Convention Center

9:00 a.m. to 5:00 p.m.

FRIDAY-MONDAY

PSYCHIATRY

Harvey Small, MD, San Mateo ..... *Chairman*
George A. Gross, MD, Sacramento ..... *Secretary*
William Holyoak, MD, Beverly Hills ..... *Assistant Secretary*

SATURDAY, FEBRUARY 22

Creativity and the Art of Medicine

Cosponsored by
American Psychiatric Association, Area VI

Moderator: George A. Gross, MD, Sacramento

1:00 **Psychiatry Section Business Meeting**

1:30 **Creativity—The Basic Factors for Art**
Frank Barron, PhD, Santa Cruz

2:00 **Iconoclastic Factors in the Art of Medicine**
Allen J. Enelow, MD, San Francisco

2:30 **Clinical Factors in the Art of Medicine**
William P. Duffy, MD, Sacramento

3:15 **Reviewing the Art of Medicine**
C. H. Hardin Branch, MD, Santa Barbara

3:45 **Discussion**

4:30 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

RADIOLOGY

Duane Blickenstaff, MD, La Jolla ..... *Chairman*
Fred Sondheimer, MD, San Francisco ..... *Secretary*
William Pogue, MD, La Mesa ..... *Assistant Secretary*

SUNDAY, FEBRUARY 23

Recent Advances in Neuroradiology

Special Focus: The EMI Computerized Brain Scan

JOINT MEETING
Section on Radiology
Section on Neurology

Cosponsored by
Los Angeles County/USC Medical Center

9:00 **EMI Scanner: Basic Techniques, Anatomy, Indications and Accuracy**
David F. Reese, MD, Rochester, Minnesota

9:40 **Question and Answer Period**

10:00 **EMI Scanner, Case Presentations**
David F. Reese, MD, Rochester

10:40 Coffee Break

11:00 **Cerebral Embolization—A Common Clinical Entity Not Commonly Recognized**
Calvin Rumbaugh, MD, Los Angeles

11:45 **Interventional Neuroradiology**
John R. Bentson, MD, Los Angeles

12:30 **Question and Answer Period**

12:55 **Radiology Section Business Meeting**

Acceptable for Category I Credit in the CMA Certification Program

UROLOGY

James Rohn, MD, Visalia ..... *Chairman*
Eugene Cattolica, MD, Oakland ..... *Secretary*
J. Bernard Miller, MD, Santa Ana ..... *Assistant Secretary*

MONDAY, FEBRUARY 24

JOINT MEETING
Section on Urology
Section on Obstetrics and Gynecology

Cosponsored by
University of California, Irvine
California College of Medicine
California Section, American College of Obstetricians and Gynecologists

$10 Reservation fee (Includes Lunch)
Please use reservation form on Page 24

8:45 **Welcome**
Charles E. Weber, MD, La Jolla
J. Bernard Miller, MD, Santa Ana

9:00 **Management of the Critically Ill Obstetrical-Gynecology or Genitourinary Patient**
Robert Baker, MD, Chicago

10:30 Coffee Break

10:45 **Genitourinary Intensive Care Unit of Los Angeles County/USC Medical Center**
Malcolm D. Cosgrove, MD, Los Angeles

11:45 **Urology Section Business Meeting**

12:15 Luncheon
Medical Legal Problems of Obstetricians and Urologists
David Rubsamen, MD, LLB, Berkeley

2:15 **Repair of Vesicovaginal Fistula—O/G Approach**
Speaker to be announced

2:45 **Repair of Vesicovaginal Fistula—G/U Approach**
Carl K. Pearlman, MD, Santa Ana

3:15 Coffee Break

3:30 **Female Sterilization**
Speaker to be announced

4:00 **Male Sterilization**
Stanwood S. Schmidt, MD, Eureka

Acceptable for Category I Credit in the CMA Certification Program

Preregistration Forms

Third Congress on Health of the School-Age Child

Luncheon and mini-session reservation

SATURDAY, FEBRUARY 23, 9:00 am

$10

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

List three choices for each session in order of preference: (See program for titles)

Morning Session: _____

_____

_____

Afternoon Session: _____

_____

_____

Please make check payable to: School Health Alliance

Return this application with total remittance to:

ROBERT DARTER, MD
P.O. Box 32
St. Helena, CA 94574

Alcoholism and Drug Dependence

Special Conference and Luncheon Reservation

SUNDAY, FEBRUARY 23, 8:30 am

$25

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

Please make check payable to: CMA Committee on Alcoholism and Other Drug Dependence

Return this application with total remittance to:

GAIL JARA
California Medical Association
731 Market Street
San Francisco, CA 94103

Allergy Section

Dinner Meeting

SATURDAY, FEBRUARY 22, 6:00 pm

$25

Breakfast Seminars

SUNDAY, FEBRUARY 23, 7:30 am

$12

Please list first and second choices: (See program for titles)

First Choice _____

Second Choice _____

Respiratory Allergy Conference and Luncheon

SUNDAY, FEBRUARY 23, 8:35 am

$15

Please reserve _____ dinner tickets at $25 each

_____ breakfast tickets at $12 each

_____ luncheon tickets at $15 each

Total Enclosed _____

Name _____

Address _____

City _____ Zip _____

Please make check payable to: CMA Section on Allergy

Return this application with total remittance to:

MR. B. E. BLACK
P.O. Box 2362
Inglewood, CA 90305

Dermatology Section

Dinner reservation

SATURDAY, FEBRUARY 22, 6:30 pm

The Los Angeles Music Center, Eldorado Room

$14 (Registration deadline February 15, 1975)

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

Please make check payable to: CMA Section on Dermatology

Return this application with total remittance to:

MARIAN BRUBAKER, MD
1346 Foothill Blvd.
La Canada, CA 91011

General Surgery Section

Luncheon meeting

FRIDAY, FEBRUARY 21, 12:00 noon

$10

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

Please make check payable to: CMA Section on General Surgery

Return this application with total remittance to:

FRED TURRILL, MD
540 North Central Ave.
Glendale, CA 91203

Pediatrics Section

Luncheon reservation

SATURDAY, FEBRUARY 22, 8:45 am

$10

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

Please make check payable to: CMA Section on Pediatrics

Return this application with total remittance to:

EDWARD J. OTTENHEIMER, MD
3939 Iowa Street
San Diego, CA 92101

Joint Meeting: Urology and Obstetrics and Gynecology Sections

MONDAY, FEBRUARY 24, 8:45 am

$10

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

Please make check payable to: CMA Sections on Urology and OB/GYN

Return this application with total remittance to:

THEODORE W. LORING, MD
2607 Harris Street
Eureka, CA 95501

Joint Meeting: Physical Medicine and Rehabilitation and Anesthesiology Sections

Special two-day conference (luncheons included)

FRIDAY, FEBRUARY 21, 8:00 am
SATURDAY, FEBRUARY 22, 8:20 am

$50

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

Please make check payable to: CMA Section on Physical Medicine

Return this application with total remittance to:

WILLIAM J. LA JOIE, MD
4305 Torrance Blvd.
Torrance, CA 90503

Plastic Surgery Section

Special Conference Reservation (Laboratory)
(Enrollment limited to 50 physicians)

MONDAY, FEBRUARY 24, 8:30 am

$25

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

Please make check payable to: CMA Section on Plastic Surgery

Return this application with total remittance to:

FREDERICK M. GRAZER, MD
1401 Avocado Avenue, Suite 502
Newport Beach, CA 92660

Ophthalmology Section

Special Conference and Luncheon Reservation

SUNDAY, FEBRUARY 23, 9:00 am

$15

Please reserve _____ tickets for:

Name _____

Address _____

City _____ Zip _____

Please make check payable to: CMA Section on Ophthalmology

Return this application with total remittance to:

JERRY DONIN, MD
1774 Alameda St.
Pomona, CA 91768

CALIFORNIA
MEDICAL ASSOCIATION

104th Annual Session
AND
Western Scientific Assembly

February 21-26, 1975 • Los Angeles Convention Center • The Biltmore Hotel, Los Angeles

Registration Opens Friday, February 21, 7:45 a.m. at the Convention Center

(A booth will be open at the hotel from Saturday through Tuesday)

SCIENTIFIC SESSIONS	Begin Friday Morning, February 21 Conclude Monday, February 24 Los Angeles Convention Center	**HOUSE OF DELEGATES**	Opening Session Saturday, February 22 Closing Session Wednesday, February 26 The Biltmore Hotel

APPLICATION FOR HOTEL ACCOMMODATIONS

Fill in the form below **completely** for room accommodations at the CMA's 1975 Annual Session.

Your reservation request should include the definite date and hour of your arrival and departure.

All reservations, except for suites, must be made through The Biltmore Hotel, 515 South Olive Street, Los Angeles 90013 **by January 21, 1975.**

All SUITE reservations must be cleared through the CMA Convention Office, San Francisco. If you are requesting a suite, direct your requests to: CMA Convention Office, 731 Market Street, San Francisco 94103.

Cancellations: Please notify The Biltmore Hotel of all cancellations.

Changes: All other changes are also to be made directly with the hotel at all times.

THE BILTMORE HOTEL

Singles	$18-22
Twins or doubles	$22-30
Additional person in room	$ 4
1 Bedroom suites	$55 and up

Send to: The Biltmore Hotel, Attn: Reservations
515 South Olive Street, Los Angeles 90013

Please reserve the following accommodations for the CMA's 1975 Annual Session:

Please Indicate Preference:

Single Bedroom $_____ Twin-Bed $_____ Double Bed $_____ Suite $_____

Arrival (date) _____ Hour _____ a.m. p.m. Departure (date) _____ Hour _____ a.m. p.m.

The name and address of each hotel guest must be listed. Include names and addresses of **each** person in a double or twin-bedded room, and names and addresses of **all other persons** for whom you are requesting reservations.

Your Name _____

Address _____ County _____

City and State _____ Zip Code _____

GUESTS' NAMES AND ADDRESSES:

_____

_____

_____

STANLEY A. MOORE
President

CARL GOETSCH
President-Elect

Officers and Delegates

GENERAL OFFICERS

Stanley A. Moore, San Diego ..... *President*
Carl Goetsch, Berkeley ..... *President-Elect*
Joseph F. Boyle, Los Angeles .. *Speaker, House of Delegates*
Henry V. Eastman, Tustin . *Vice-Speaker, House of Delegates*
E. Kash Rose, Napa ..... *Chairman of the Council*
Frederick W. Ackerman,
Concord ..... *Vice-Chairman of the Council*
Thomas Elmendorf, Davis ..... *Immediate Past President*
Albert G. Clark, San Francisco ..... *Secretary*
Malcolm S. M. Watts, San Francisco ..... *Editor*
Willis W. Babb ..... *Executive Director*
Hassard, Bonnington, Rogers & Huber ..... *Legal Counsel*

House of Delegates

TOTAL VOTING MEMBERS (337)

OFFICERS

Voting (9)

Stanley A. Moore, San Diego ..... President
Carl Goetsch, Berkeley ..... President-Elect
Joseph F. Boyle, Los Angeles ..... Speaker, House of Delegates
Henry V. Eastman, Tustin ..... Vice-Speaker, House of Delegates
E. Kash Rose, Napa ..... Chairman of the Council
Frederick W. Ackerman, Concord ..... Vice-Chairman of the Council
Thomas Elmendorf, Davis ..... Immediate Past President
Albert G. Clark, San Francisco ..... Secretary
Malcolm S. M. Watts, San Francisco ..... Editor

COUNCILORS

Voting (24) (3 voting as officers)

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Office No. 1, Gladden V. Elliott ..... (1976)
Office No. 2, Harvey O. Randel ..... (1977)

SECOND DISTRICT—Nicholas P. Krikes ..... (1977)

THIRD DISTRICT—
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Office No. 2, Marshall P. Stonestreet ..... (1976)

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Office No. 2, Jokichi Takamine ..... (1977)
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Office No. 7, George C. Andersen ..... (1977)
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SIXTH DISTRICT—
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SEVENTH DISTRICT
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Office No. 2, Howard W. Lindsey ..... (1977)
Office No. 3, Eugene E. Eldredge ..... (1977)

EIGHTH DISTRICT—
Office No. 1, Albert G. Clark ..... (1975)
Office No. 2, Sanford E. Feldman ..... (1976)

NINTH DISTRICT—
Office No. 1, William G. Donald ..... (1975)
Office No. 2, Frederick W. Ackerman ..... (1976)

TENTH DISTRICT—E. Kash Rose ..... (1976)

ELEVENTH DISTRICT—Orrin S. Cook ..... (1975)

TWELFTH DISTRICT—Forest J. Grunigen ..... (1976)

SCIENTIFIC BOARD REPRESENTATIVE—C. John Tupper ..... (1976)

SCIENTIFIC BOARD

Ex officio, Non-voting (22)

Delegates	Alternates
(Not available at press time)	

PAST PRESIDENTS

Ex officio, Non-voting (23)

Molony, William R., Sr.	1942	Sherman, Samuel R.	1963
Scheupp, Karl L., Sr.	1943	Doyle, James C.	1964
Askey, E. Vincent	1948	Teall, Ralph C.	1965
Cass, Donald	1950	MacLaggan, James C.	1966
Green, John W.	1953	Morrison, John G.	1967
Morrison, Arlo A.	1954	Todd, Malcolm C.	1968
Shipman, Sidney J.	1955	Miller, Albert G.	1969
MacDonald, Frank A.	1957	Burnett, Ralph W.	1970
West, Francis E.	1958	Fenlon, Roberta F.	1971
Reynolds, T. Eric	1959	Crum, Jean F.	1972
Foster, Paul D.	1960	Elmendorf, Thomas	1973
Bostick, Warren L.	1961		

HONORARY PAST PRESIDENT

Ex officio, Non-voting (1)

Dwight L. Wilbur

SPEAKER EMERITUS

William F. Quinn

CMA DELEGATION TO THE AMA

Ex officio, Non-voting (26)

Delegation Office Number	Delegate	Alternate
	FIRST DISTRICT	
1	**James C. MacLaggan** San Diego 1-1-74 to 12-31-75	**Stewart Dadmun** San Diego 1-1-75 to 12-31-76
2	**Elmer C. Werner** El Centro 1-1-74 to 12-31-75	**Stanley A. Moore** La Jolla 1-1-74 to 12-31-75
	SECOND DISTRICT	
3	**Herman H. Stone** Riverside 1-1-75 to 12-31-76	**Nicholas P. Krikes** San Bernardino 1-1-74 to 12-31-75
	THIRD DISTRICT	
4	**Vincent P. Carroll** Legune Beach 1-1-74 to 12-31-75	**Laurance A. Mosier** Garden Grove 1-1-74 to 12-31-75
25	**Robert C. Combs** Irvine 1-1-73 to 12-31-74	**Henry V. Eastman** Tustin 1-1-74 to 12-31-75
	FOURTH DISTRICT	
5	**Jean F. Crum** Downey 1-1-75 to 12-31-76	**David B. Horner** Inglewood 1-1-74 to 12-31-75
6	**Frank A Rogers** Whittier 1-1-74 to 12-31-75	**Walter R. Buerger** Covina 1-1-75 to 12-31-76
7	**David I. Olch** Los Angeles 1-1-75 to 12-31-76	**Donald A. Adams** Los Angeles 1-1-75 to 12-31-76
8	**Joseph P. O'Connor** Pesadene 1-1-74 to 12-31-75	**H. Russell Fisher** Glendale 1-1-75 to 12-31-76
9	**Ralph M. Milliken** Los Angeles 1-1-75 to 12-31-76	To be elected 6-75
10	**Marvin J. Shapiro** Encino 1-1-74 to 12-31-75	**Jack E. McCleary** Sherman Oaks 1-1-75 to 12-31-76
11	**Edward J. Wiater** Long Beech 1-1-75 to 12-31-76	**George Evashwick** Long Beach 1-1-75 to 12-31-76
12	**Joseph F. Boyle** Los Angeles 1-1-75 to 12-31-76	**Raymond N. F. Killeen** Los Angeles 1-1-74 to 12-31-75
13	**Jokichi Takamine** Los Angeles 1-1-75 to 12-31-76	To be elected 6-75
	FIFTH DISTRICT	
14	**Harry J. Fryer** San Luis Obispo 1-1-74 to 12-31-75	**R. John Rutten** Santa Barbera 1-1-75 to 12-31-76
	SIXTH DISTRICT	
15	**Robb Smith** Orange Cove 1-1-73 to 12-31-74	**Arthur F. Howard** Fresno 1-1-74 to 12-31-75
16	**Ralph W. Burnett** Bakersfield 1-1-73 to 12-31-74	**David S. Ardell** Bakersfield 1-1-73 to 12-31-74
	SEVENTH DISTRICT	
17	**Leon P. Fox** San Jose 1-1-75 to 12-31-76	**Dan W. Clark** San Jose 1-1-75 to 12-31-76
18	**John T. Saidy** San Mateo 1-1-74 to 12-31-75	**Howard W. Lindsey** San Mateo 1-1-75 to 12-31-76
26	**R. Hewlett Lee** Palo Alto 1-1-74 to 12-31-75	**Thomas Elmendorf, at-large*** Davis 1-1-74 to 12-31-75
	EIGHTH DISTRICT	
19	**George K. Herzog, Jr.** San Francisco 1-1-74 to 12-31-75	**Xavier O. Barrios** San Francisco 1-1-74 to 12-31-75
20	**Edward T. Kelley** San Francisco 1-1-74 to 12-31-75	**Brad Cohn** San Francisco 1-1-74 to 12-31-75
	NINTH DISTRICT	
21	**Herold Kay** Oakland 1-1-74 to 12-31-75	**Herbert A. Holden** San Leandro 1-1-74 to 12-31-75
22	**John G. Morrison** Sen Leendro 1-1-73 to 12-31-74	**Frederick W. Ackerman** Concord 1-1-73 to 12-31-74
	TENTH DISTRICT	
23	**A. Hainan White** Kentfield 1-1-75 to 12-31-76	**Raymond C. Anderson** Irvine 1-1-74 to 12-31-74
	ELEVENTH DISTRICT	
24	**Ralph C. Teall** Secremento 1-1-74 to 12-31-75	**Franklin L. Murphy** Oroville 1-1-75 to 12-31-76

*At the expiration of "at-large" term, the office reverts to District 7.

Reports of officers, commissions and committees of the California Medical Association, together with the audited financial statements for the fiscal year ended June 30, 1974, are printed in the *Annual Reports Bulletin,* which is distributed to CMA Delegates and Alternates before the meeting of the House of Delegates. The *Bulletin* is also available to any member of the Association on request directed to Executive Director, California Medical Association, 731 Market Street, San Francisco, California 94103.

DISTRICT DELEGATIONS AND CHAIRMEN

FIRST DISTRICT — **Robert T. Plumb**
Imperial and San Diego Counties

SECOND DISTRICT — **Harrison E. Silver**
Inyo, Mono, Riverside and San Bernardino Counties

THIRD DISTRICT — **Richard F. Altman**
Orange County

FOURTH DISTRICT — **Edward J. Wiater**
Los Angeles County

FIFTH DISTRICT — **Charles Reach**
San Luis Obispo, Santa Barbara and Ventura Counties

SIXTH DISTRICT — **Robert Purvis**
Amador, Calaveras, Fresno, Kern, Kings, Madera, Mariposa, Merced, San Joaquin, Stanislaus, Tulare and Tuolumne Counties

SEVENTH DISTRICT — **Ward L. Hart**
Monterey, San Benito, San Mateo, Santa Clara and Santa Cruz Counties

EIGHTH DISTRICT — **John A. Driscoll**
San Francisco County

NINTH DISTRICT — **Bruce M. Anderson**
Alameda and Contra Costa Counties

TENTH DISTRICT — **William Waring**
Del Norte, Humboldt, Lake, Marin, Mendocino, Napa, Solano and Sonoma Counties

ELEVENTH DISTRICT — **John R. Heckman**
Alpine, Butte, Colusa, El Dorado, Glenn, Lassen, Modoc, Nevada, Placer, Plumas, Sacramento, Shasta, Sierra, Siskiyou, Sutter, Tehama, Trinity, Yolo and Yuba Counties

TWELFTH DISTRICT
Forty First Medical Society

ELECTED DELEGATES (294)

Delegates	Alternates
ALAMEDA-CONTRA COSTA (22)	
(Not available at press time)	
BUTTE-GLENN (2)	
(Not available at press time)	
FORTY FIRST (2)	
Grunigen, Forest J.	
FRESNO (6)	
(Not available at press time)	
HUMBOLDT-DEL NORTE (2)	
(Not available at press time)	
IMPERIAL (2)	
(Not available at press time)	
INYO-MONO (2)	
(Not available at press time)	
KERN (4)	
(Not available at press time)	
KINGS (2)	
(Not available at press time)	
LASSEN-PLUMAS-MODOC-SIERRA (2)	
(Not available at press time)	
LOS ANGELES (90)	
Adams, Donald A.	Alban, Seymour L.
Affley, Harry J., Jr.	Alexakis, Peter G.
Alter, Marvin S.	Baker, Francis J.
Amerongen, Frederick K.	Belt, Robert L.
Aquila, S. J.	Bertolino, James
Asher, Leonard M.	Birnberg, Victor J.
Axelrod, Bernard	Blackman, Burton T.
Baker, Jack W.	Bland, Stephen L.
Basque, W. David	Bower, Paul L.
Bergreen, Stanley W.	Bradley, Gerald H.
Blood, William B.	Breen, David S.
Bowen, Gordon T.	Brien, Stuart
Brennan, James E.	Bruckner, Sherman H.
Buehler, George S.	Butler, Edwin W.
Buerger, Walter R.	Campion, George M.
Butler, R. Melvin	Carney, Padraig
Carroll, Robert L.	Chusid, Lawrence A.
Chasan, Fred	Colbert, Edward G.
Chiang, Ching H.	Cooperman, Howard
Crumrine, Martin H.	Creary, Ludlow B.
del Junco, Tirso	Critchlow, Francis B.
DeMangus, Robert X.	Crivaro, John P.
Donoghue, Charles K.	Dahl, David J.
D'Orazio, Edward	Dashe, Alfred M.
Dorn, Robert M.	Dickes, Richard E.
Evashwick, George	Diehl, John W.
Fields, Albert	Diess, Neil E.
Ford, James H.	Duckworth, R. Ray
Frank, William P.	Edwards, John W.
Freidin, Morris	Fraser, Gordon C.
Fritz, Samuel H.	Goldman, Leonard
Gordon, Irving J.	Hart, Rinard Z.
Greco, Donald J.	Heiser, Saul
Greenberg, Paul M.	Hellinger, Bernard S.
Guiss, Lewis W.	Hoffman, Warren F.
Harter, Melvin M.	Holder, Richard M.
Hartleip, Duane L.	Holtz, Marvin J.
Haskell, M. M.	Hoyos, Jorge
Hemsley, Hubert L.	Hyman, William
Hill, Harry E.	Japenga, Jack W.
Hoffman, Peter L.	Jenkins, Charles E.
Horner, David B.	Kaspar, Friedrich H.
Johnson, Robert M.	Katz, Edward E.
Kaminski, Kenneth L.	Keenan, Charles E., Jr.
Karlan, Mitchell S.	Krause, Melvyn H.
Karns, Robert M.	Llanos, Miguel A.
Kaufman, Gene B.	Maloney, James V., Jr.
Kaufmann, Bertram J., Jr.	Margolin, Malcolm L.
Ketcham, Burton E., Jr.	Marr, James C., Jr.
Killeen, Raymond N. F.	Marx, Frederick W., Jr.
Kremen, Samuel	Mazurek, Richard J.
Kugel, Arthur I.	McElwee, Charles B.
Kuhn, Robert	McRae, John A.
Lau, Michael W.	Menze, Jackson S.
Lopez, Charles J.	Michels, Arthur G.
McCaffery, James M.	Mizener, Wilson
Mailman, Richard H.	Moore, Rolet A.
Martini, M. Michael	Morgan, Henry G.
May, Lewis H. V.	Murphy, Terrence J.
Meine, Emile L., Jr.	Nehorayan, S. Saul
Miller, Richard D.	Noguchi, Thomas T.
Murrieta, A. J., Jr.	Okie, Theodore B.
Neuenschwander, Robert S.	Pallette, Edward M.
Newhouse, Robert M.	Papatheodorou, Christos A.
Odou, Eugene R.	Rago, Marco R.
Olch, David I.	Reager, Lauren L.
Palmer, Jay J.	Redewill, Francis H., Jr.
Penka, Ernest J.	Richards, Melvin R.
Penn, Sidney W.	Sanchez, Alphonso R.
Pettit, Richard D.	Schaefer, E. Lowell
Pollack, John V.	Schmit, Robert A.
Rockney, Robert E.	Seidman, Donald R.
Rolf, Bruce B.	Sibley, Willie F.
Rothenberg, Sanford F.	Siegel, Joseph A.
Rubell, Earl B.	Slater, Roger A.
Sewak, John H.	Spierer, Eugene
Smith, Thayer A.	Stanton, Ernest M.
Todt, Jack C.	Stauffer, Floyd R.
Trumbull, William E.	Steen, Alan M.
van Adelsberg, Stephan B.	Tashma, Albert
Watson, Robert L., Jr.	Todd, William H.
Weil, William S.	Tremblay, Wyman C.
Weiss, Benjamin J.	Tudbury, Patricia B.
White, John R.	Valvo, Carlton F.
Wiater, Edward J.	Westerbeck, Charles W.
Wigton, John R.	Wong, Alton S. K.
Williams, Henry S.	Wright, Carter R., Jr.
Wong, Thomas A.	Yamaguchi, Donald M.
Wunderlich, Edwin E.	Zinn, Willard J.
Zinn, Alexander N.	Zwemer, Theodore W.
MARIN (4)	
Costanza, David	Belknap, Marjorie
Franzblau, Michael	Burke, Mervyn
Tavel, Frank	Hoffman, Charles
White, A. Halnan	Lesko, Clarence
MENDOCINO-LAKE (2)	
(Not available at press time)	

Delegates	Alternates
MERCED-MARIPOSA (2)	
Mansur, G. Philip	Bessemer, Raymond
Warren, Donald J.	Rugani, Peter R.
MONTEREY (4)	
(Not available et press time)	
NAPA (2)	
Hemphill, Arthur C.	Nelson, Robert A.
Queary, Charles H.	Waechtler, Herbert W.
ORANGE (17)	
(Not available at press time)	
PLACER-NEVADA (2)	
Johnson, F. Harold	Anthony, William
Sweeney, George	Henderson, Charles C.
RIVERSIDE (5)	
(Not available et press time)	
SACRAMENTO (9)	
(Not available at press time)	
SAN BENITO (2)	
(Not available et press time)	
SAN BERNARDINO (7)	
Allen, Byron	Ballard, Ross L.
Hendrickson, Merlin A.	Kuhn, Irvin
Johns, Varner	McAllister, John
Mortensen, John	Orr, Horace
Moseley, Wendell	Robinson, Hurley
Wake, Donald K.	Talbert, Myron
White, Eugene	Taurek, Jerome
SAN DIEGO (17)	
(Not available at press time)	
SAN FRANCISCO (20)	
Allen, David W.	Adams, Donald R.
Barrios, Xavier O.	Biskind, Gerson R.
Cohn, Brad	Davis, Harold
Cook, Robert E.	Dulay,Fernando V.
Driscoll, John A.	Foster, Sidney E.
Gordon, Robert B.	Frenkenberg, Andre M. M.
Kelley, Edward T.	Hayden, Ralph O.
Lee, Jane F.	Henderson, John C.
Lindner, Harold H.	Kucera, Gilbert J.
Molyneaux, Glenn	Lesko, Louis
Oscherwitz, Mark	Low, Serene C.
Palmer, Richard J.	Noltheimer, Louis A.
Paver, Robert L.	Pennell, Willard H.
Phipps, James W.	Pevehouse, Byron C.
Pillsbury, Philip L.	Salomon, Maurice S.
Sachs, David D.	Saunders, John B. de C. M.
Solari, Rafael A.	Scholten, Paul
Wayburn, Edgar	Sherman, Robert S., Jr.
Weinreb, Irwin	Schaffarzick, Ralph W.
Wray, H. Wesley	Zarate, Eugenio A.
SAN JOAQUIN (4)	
Clark, Stanley A., Jr.	Chimiklis, Arthur
McNally, John T.	Hoff, Helmuth
Shinn, William	Kimball, John
Wass, Warreen	Serre, Joseph
SAN LUIS OBISPO (2)	
Cletsoway, Richard W.	Jorgensen, Jerren
Osibin, Willard S.	McAdams, Brenden V.
SAN MATEO (8)	
Bell, Leo S.	Breit, Arnold J.
Geraci, Charles L.	Feinstein, Myron S.
Hart, Ward L.	Hales, Donald R.
Healy, Francis A.	Marquette, Richard H.
Hills, Oscar W.	Nagumo, Saburo
Johnson, Harold P., Jr.	O'Meara, M. Patrick
Packard, Peter	Sarconi, John A.
Richanbach, Henry S.	Richards, Marvin D.

Delegates	Alternetes
SANTA BARBARA (5)	
(Not available at press time)	
SANTA CLARA (15)	
Armstrong, Frederick S.	Adams, Deane T.
Burnett, Robert D.	Austin, Glenn
Drinker, Henry R., Jr.	Bright, Ross D.
Fox, Leon P.	Dolan, Michael P.
Giansiracusa, Frank J.	Elliott, Hugh W.
Grossman, Maurice	Gherini, Allan J.
Lee, R. Hewlett	Kornfield, Harrison J.
McCort, James J.	Lasnover, Alan L.
Neubauer, Ivan C.	Lippe, Philipp M.
O'Neill, Robert J.	Marlow, John E.
Rowles, Donald F.	Rappaport, Maurice
Scarborough, C. Gerald	Reeves, William A.
Truitt, Robert B.	Rodenbaugh, F. Hese
Whelan, Harry G.	Upton, Hubert M.
Zlotnick, David A.	Williams, James H.
SANTA CRUZ (3)	
(Not available at press time)	
SHASTA-TRINITY (2)	
(Not available at press time)	
SISKIYOU (2)	
Christy, John R.	Klatt, Lloyd I.
Howe, Roger	Lund, Johenna E.
SOLANO (2)	
Gullock, Alvin H.	Miller, John C.
Lonsdale, Howard C.	Vincent, Keith E.
SONOMA (4)	
Archambeau, Paul L.	LeStovic, Joseph J.
Gary, Stephen C.	
Lones, Frank E.	
Olney, John M.	
STANISLAUS (4)	
Bigelow, Wayne	Benak, Steve
McKibben, J. W.	Lanfranki, John
Nyegaard, Roland C.	Stocks, Laurence O.
Purvis, Robert W.	Walton, Robert G.
TEHAMA (2)	
(Not available at press time)	
TULARE (3)	
(Not available at press time)	
VENTURA (4)	
(Not available et press time)	
YOLO (3)	
Odland, T. M.	Hanson, G. R.
Wilson, B. Kent	Palmer, John
Winn, Dean F., Jr.	Stice, Charles, W.
YUBA-SUTTER-COLUSA (2)	
(Not available at press time)	
HOUSE OFFICER COMPONENT UNIT (2)	
(Not available at press time)	
MEDICAL STUDENTS (8)	
Henrichs, Charles Loma Linda	Sheehan, Dennis Loma Linda
Resnick, Neil Stanford	Palmer, Gary Stanford
Schmitt, William UC-Davis	(NA et press time) UC-Davis
Acord, Michael UC-Irvine	Granger, Eugene UC-Irvine
Scherger, Joseph UCLA	Oppenheim, Gene UCLA
Ahlering, John UC-San Diego	(NA at press time) UC-San Diego
Denney, Philip USC	Feinstein, Barney USC
Chadek, Christine UC-San Francisco	Gelb, Alan UC-Sen Francisco

1975 Annual Session
House of Delegates

AGENDA

Biltmore Bowl, Los Angeles Biltmore Hotel

Joseph F. Boyle, Los Angeles ..... *Speaker*
Henry V. Eastman, Tustin ..... *Vice-Speaker*
Albert G. Clark, San Francisco ..... *Secretary*

SATURDAY, FEBRUARY 22, First Meeting

REGISTRATION—12:00 noon
MEETING STARTS—1:00 p.m. Sharp

1. Call to order (Invocation and Pledge of Allegiance)
2. Announcement of Reference Committees*
   - Committee on Credentials
   - Reference Committee A—Community and Environmental Health
   - Reference Committee B-1—Government Medical Programs
   - Reference Committee B-2—Government Medical Programs
   - Reference Committee C-1—Medical Economics, Insurance and Prepayment
   - Reference Committee C-2—Medical Economics, Insurance and Prepayment
   - Reference Committee D-1—Scientific and Educational Activities
   - Reference Committee D-2—Scientific and Educational Activities
   - Reference Committee E-1—Professional and Public Relations
   - Reference Committee E-2—Professional and Public Relations
   - Reference Committee F—Finance
   - Reference Committee G—Constitution and Bylaws
   - Reference Committee H—Blue Shield of California
3. Miscellaneous Announcements
4. Honored Guests
5. Report of the Committee on Credentials, and Organization of the House of Delegates—Roll Call
6. Recognition of President of Woman's Auxiliary to the CMA—Mrs. Harry S. Dvorsky
7. Address by President—Stanley A. Moore
8. Report of the President—Stanley A. Moore
9. Report of the President-Elect—Carl Goetsch
10. Report of the Speaker and Vice-Speaker of the House of Delegates—Joseph F. Boyle and Henry V. Eastman
11. Report of the Trustees of the California Medical Association—Stanley A. Moore
12. Report of the Physicians' Benevolence Fund, Inc.—Stanley A. Moore
13. Report of the Secretary—Albert G. Clark
14. Report of the Editor—Malcolm S. M. Watts
15. Report of the Executive Director—Willis W. Babb
16. Report of Legal Counsel—Hassard, Bonnington, Rogers & Huber
17. Report of the Executive Committee—Stanley A. Moore
18. Report of the Council—E. Kash Rose, Chairman
19. Report of Blue Shield of California Trustees—Marvin J. Shapiro, Chairman
20. Reports of Commissions
21. Reports of other Committees
22. Old and unfinished business
23. New business
24. Adjournment

*Subject to revision

TUESDAY, FEBRUARY 25, Second Meeting

REGISTRATION—12:00 noon
MEETING STARTS—1:30 p.m.

(To be recessed and reconvened at 9:00 a.m., Wednesday, February 26)

1. Call to order
2. Supplemental Report of Credentials Committee—Roll Call
3. Address by President-Elect—Carl Goetsch
4. Introduction of President-Elect of Woman's Auxiliary to the CMA—Mrs. Salvadore A. Lask
5. Secretary's announcement of Council's selection of time and place for the 1976 Annual Session
6. Election of Officers
7. Announcement of nominations of Delegates and Alternates to the American Medical Association
8. Election of Blue Shield of California Trustees
9. Reports of Reference Committees
10. Unfinished business
11. New business
12. Presentation of Officers
13. Adjournment

FOR ACTION IN 1975

Three Constitutional amendments were introduced in the 1974 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates, and must be published twice before they come before the House of Delegates for action.

ARTICLE III, PART B, SECTION 9. COMPOSITION

Introduced by: Council
Representing: Council
Author: E. Kash Rose, MD

Constitutional Amendment No. 1-74
Committee G

Resolved: That Article III, Part B.—Council.—Section 9.—Composition be amended by deleting the words in brackets and adding the words in italics, so that this section shall now read:

The Council shall consist of:

(a) Elected councilors from the councilor districts set forth in Section 10. Each councilor district shall be entitled to elect one councilor for each 1,000 active members, or major fraction thereof, according to its membership as of the first day of September of the preceding year; provided, that each councilor district shall be entitled to a minimum of one councilor.

(b) Elected councilors from any one district shall not, at any time, exceed 40 percent of the total Council membership.

(c) The president, president-elect, immediate past president,[10] speaker and vice-speaker.

[(d) The secretary, *who shall be selected from the Council* and editor, when they are members of the Association, shall be ex officio members of the Council without the right to vote.[11]]

[e] *(d)* The editor, when [they are members] *he is a member* of the Association, shall be *an* ex officio member[s] of the Council without the right to vote.

[f] *(e)* One member of the Executive Committee of the Scientific Board, who shall be elected by the Scientific Board from representatives of the scientific sections or members-at-large, who shall be an ex officio member of the Council with the right to vote.

ACTION: Tabled for one year; to be acted upon at the 1975 meeting of the House of Delegates.

ARTICLE III, PART B, SECTION 11. ELECTION OF COUNCILORS

Introduced by: Council
Representing: Council
Author: E. Kash Rose, MD

Constitutional Amendment No. 2-74
Committee G

Resolved: That Article III, Part B, Section 11, be amended, to read:

District councilors shall be elected [by vote of the delegates from each district] in the manner and at the time specified in the Bylaws; provided, however, that at the first meeting of the House of Delegates after a district councilor has been selected, his name shall be submitted to the House by the delegates from the district, and (1) if there is no challenge by any delegate then the speaker shall declare his election completed, and (2) if any delegate shall challenge the election on any ground, including fitness of the nominee of the district to serve as a district councilor, the questions presented by the challenge shall be submitted to a Qualifications Committee consisting of the president, president-elect and one delegate, appointed by the speaker, from the councilor district involved. The Qualifications Committee shall consider all grounds upon which the nominee is challenged and report back to the House. If the committee reports in favor of confirming the nominee's election, the speaker shall declare him elected. If the committee reports against confirming the nominee's election, a three-fourths (¾) affirmative vote shall be necessary to sustain the report of the committee, in which event the nominee shall be ineligible to serve as district councilor and the delegates from the district shall immediately proceed to the selection of another nominee for the vacant office. If an adverse report of the Qualifications Committee is not sustained then the nominee shall be declared elected by the speaker.

ACTION: Tabled for one year; to be acted upon at the 1975 meeting of the House of Delegates.

* * *

ARTICLE III, PART B, SECTION 12. COUNCILORS: TERMS OF OFFICE

Introduced by: Council
Representing: Council
Author: E. Kash Rose, MD

Constitutional Amendment No. 3-74
Committee G

Resolved: That Article III, Part B, Section 12, be amended, to read:

Section 12. Councilors: Terms of Office. Councilors shall serve for terms of three (3) years; [one-third (⅓) to be elected in each year] except that the initial term of a new office arising hereunder may be for less than three (3) years, as the Bylaws may provide, to allow for staggering of terms. A councilor shall not serve more than three (3) consecutive terms of office.

ACTION: Tabled for one year; to be acted upon at the 1975 meeting of the House of Delegates.

MRS. HARRY S. DVORSKY
President

MRS. SALVADORE A. LASK
President-Elect

Woman's Auxiliary

Forty-Fifth Annual Convention

FEBRUARY 22-25, 1975

Headquarters: Biltmore Hotel, Los Angeles

"Schedule in Brief"

(Subject to change)

Mrs. John R. Black ..... *Chairman*
Mrs. Mathew E. O'Keefe ..... *Co-Chairman*

REGISTRATION—Galeria Room

Saturday, February 22—12 noon to 4:00 p.m.
Sunday, February 23—9:00 a.m. to 4:00 p.m.
Monday, February 24—7:30 a.m. to 4:00 p.m.
Tuesday, February 25—8:00 a.m. to 10:00 a.m.

SATURDAY, February 22—Pre-Convention

1:00 p.m. Presentation of Mrs. Harry S. Dvorsky, Auxiliary President, to CMA House of Delegates, Biltmore Bowl

4:00 p.m. Executive Committee Meeting, President's Suite

SUNDAY, February 23

10:30 a.m. District Councilors Meeting, Convention Suite

1:00 p.m. Pre-Convention Board Meeting, Conference Room No. 4

6:30 p.m. Presidents' Reception, Gold Room

7:30 p.m. CMA/WA-CMA Dinner, Biltmore Bowl

MONDAY, February 24

8:30 a.m. Opening Session of House of Delegates, Biltmore Bowl

11:30 a.m. Presidents' Luncheon, Crystal Ballroom

1:30 p.m. Afternoon Session of House of Delegates, Biltmore Bowl

5:30 p.m. Evening on the Town—Shopping and dinner with your friends at the Broadway Plaza

TUESDAY, February 25

8:30 a.m. Final Session of House of Delegates, Biltmore Bowl
Installation of Officers

1:00 p.m. Orientation Meeting, Music Room

1:30 p.m. Presentation of Mrs. Salvadore A. Lask, Incoming President, to the CMA House of Delegates, Biltmore Bowl

4:00 p.m. Post-Convention Board Meeting, Music Room

HOSPITALITY CENTER—Galeria Room

Sunday, February 23—9:00 a.m. to 4:00 p.m.
Monday, February 24—7:30 a.m. to 4:00 p.m.
Tuesday, February 25—7:30 a.m. to 12:00 noon

Rolls and coffee served 7:30 a.m. to 8:30 a.m. Monday and Tuesday

A half-ounce of prevention

Use it to prevent a topical infection. Or to treat one that's already started. In either case, it's good medicine. Whether for lacerations, burns, open wounds, IV catheter or surgical aftercare. Neosporin® Ointment provides broad antibacterial coverage against common susceptible pathogens. And since it contains three antibiotics that are rarely used systemically, the risk of sensitization is reduced. Neosporin Ointment. A half-ounce of prevention. Also available in a full ounce of prevention and in convenient foil packets.

Neosporin Ointment carried on Apollo and Skylab missions.

Neosporin® Ointment
(polymyxin B-bacitracin-neomycin)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs.
In tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

INDICATIONS: *Therapeutically*, used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.
Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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Copy for classified advertisements should be received not later than **the fifth of the month preceding issue.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

GP WANTED: Southern California, Orange County. Three-man clinic long established industrial and private practice, seeking replacement for member rejoining service. Minimal cost, good net, excellent hours. Permanent association desired on expense sharing basis. California license necessary. Open approximately January 1, 1975. Write Box No. 9402, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

UNIVERSITY OF CALIFORNIA HOSPITALS & CLINICS, SAN FRANCISCO—immediate need for Medical Director of Screening and Acute Care Clinic. Must be board eligible or certified in Internal Medicine or Family Practice. Clinic provides screening and acute non-emergent care for adult self-referred patients and thus serves as entry point for many patients into the University Clinics system. Full-time equivalent position. Salary $28,500/year with adjustments consistent to qualifications and experience. For further information contact: Dr. Joseph C. Barbaccia, Associate Professor, University of California, San Francisco, CA 94143, or call (415) 666-4061.

ORTHOPEDIST: Board certified or board eligible, for large multispecialty group. Department currently consists of seven orthopedists. Department and area expanding. Edward H. Start, MD, Chief of Orthopedics, The Permanente Clinic, 5055 North Greeley Ave., Portland, Oregon 97217.

PUBLIC HEALTH PHYSICIAN

New position in a progressive county health department having 80 employees. Will head the county child health and disability prevention program. Activities will include program planning, administration, staff supervision, community outreach and screening activities, and the providing of early and periodic assessments of the health status of children for the early identification and referral for treatment of those with potential handicapping and/or disabling conditions.

Salary in range of $26,460 to $32,160 per year with anticipated increase of about 10% effective 12/1/74, or one may work on contract basis with higher income. Very pleasant, modern working environment, generous employee benefits, five day-40 hour week, and semi-rural, centrally located community of 100,000. Must be California licensed, or license eligible, with one year of experience in providing, administering, or planning health services specifically for children. ,

Contact:

C. O. SHEPHEARD
Stanislaus County Personnel Office
Room 305, Courthouse
1100 "I" Street
Modesto, CA 95354
or phone collect: (209) 526-6341

PHYSICIANS WANTED

PROGRESSIVE RURAL GROUP PRACTICE—Located in the Salinas Valley near MONTEREY and CARMEL has an immediate need for two Family Practitioners and an Internist (Generalist) to join an established 9-man group practice, plus 11 consultants, Incorporated in 1970. Competitive starting salary and top fringe benefits. Brochure by return mail. Please call or send C.V. to: DUANE F. HYDE, MD, Southern Monterey County Medical Group (A Professional Corporation), 210 Canal St., King City, CA 93930, Tel. (408) 385-5471.

FULL-TIME EMERGENCY CARE position with pre-payment group. Includes both hospital and clinic emergency care work. Partnership after two years. Excellent insurance and retirement programs. Robert A. McFarlane, MD, 5055 North Greeley Ave., Portland, Ore. 97217.

CARDIOLOGIST—Board certified internist with subspecialty in cardiology needed for busy cardiology practice in Orange County, with excellent facilities and adjacent medical school. Send résumé to Box 9392, Western Journal of Medicine, 731 Market St., San Francisco, 94103.

STEINBECK COUNTRY: Innovative, progressive rural group practice located in the Salinas Valley has an immediate need for 2 Family Practitioners, a Pediatrician and an Internist with broad-based capabilities. In addition to 9 full-time physicians, the group has 11 consultants, representing a wide spectrum of the specialties, visiting on a routine basis. University affiliation with on-site teaching. Top fringe benefits, including competitive starting salary (1st year minimum of $34,000 guaranteed), and early affiliation. Brochure by return mail. Please call or send C.V. to: Duane F. Hyde, MD, Southern Monterey County Medical Group (A Professional Corporation), 210 Canal Street, King City, CA 93930; (408) 385-5471.

UROLOGIST: Board Certified or Board Eligible. 200-bed GM&S Hospital in San Francisco Bay Area. Salary to $36,000 depending on qualifications, supplemented by attractive benefits; retirement, life and health insurance, liberal leave system; opportunity for medical school affiliation; provisions for paid continuing education programs. An equal opportunity employer. Contact Chief, Surgical Service, Veterans Administration

ORTHOPEDIST: Board Certified or Board Eligible. 200-bed GM&S Hospital in San Francisco Bay Area. Salary to $36,000 depending on qualifications, supplemented by attractive benefits: Retirement, life and health insurance, liberal leave system; opportunity for medical school affiliation; provisions for paid continuing education programs. An equal opportunity employer. Contact Chief, Surgical Service, Veterans Administration Hospital, Livermore, CA 94550. (415) 447-2560.

PHYSICIAN to direct County Child Health and Disability Prevention Program. Should have at least one year's experience in providing services to children or possess a graduate degree in Public Health. $30,000 per year plus travel. Contact Owen A. Kearns, MD, Kern County Health Officer, P.O. Box 997, Bakersfield, CA 93302; (805) 861-3655.

CLINIC PHYSICIAN IN HEALTH DEPARTMENT . . . Immediate vacancy physician who possesses California license needed to conduct out-patient clinics, participate in child health conferences, family planning, communicable disease and immunization clinics. Competitive salary and top fringe benefits. Contact O. A. Kearns, MD, Health Officer, Kern County Health Department, P. O. Box 997, Bakersfield, California 93302, or call (805) 861-3655.

GENERAL SURGEON — Staff position available for Board qualified or certified General Surgeon interested in teaching and resident and intern supervision in four-year fully approved clinically oriented general surgical residency program. Active teaching program; 350-bed county hospital with full-time Board Certified General Surgeon as Chairman of Department of Surgery. Active services include thoracic and cardiovascular surgery, neurosurgery, orthopedics, urology and plastic surgery under direction of Board Certified specialists. Salary $45,000 annually. Must be eligible for California license. Contact John Watts, MD, Chairman, Dept. of Surgery, Kern General Hospital, 1830 Flower, Bakersfield, CA 93305; (805) 323-7651.

(Continued on Page 34)

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ephedrine and theophylline relax bronchial musculature to open airways and keep them open.

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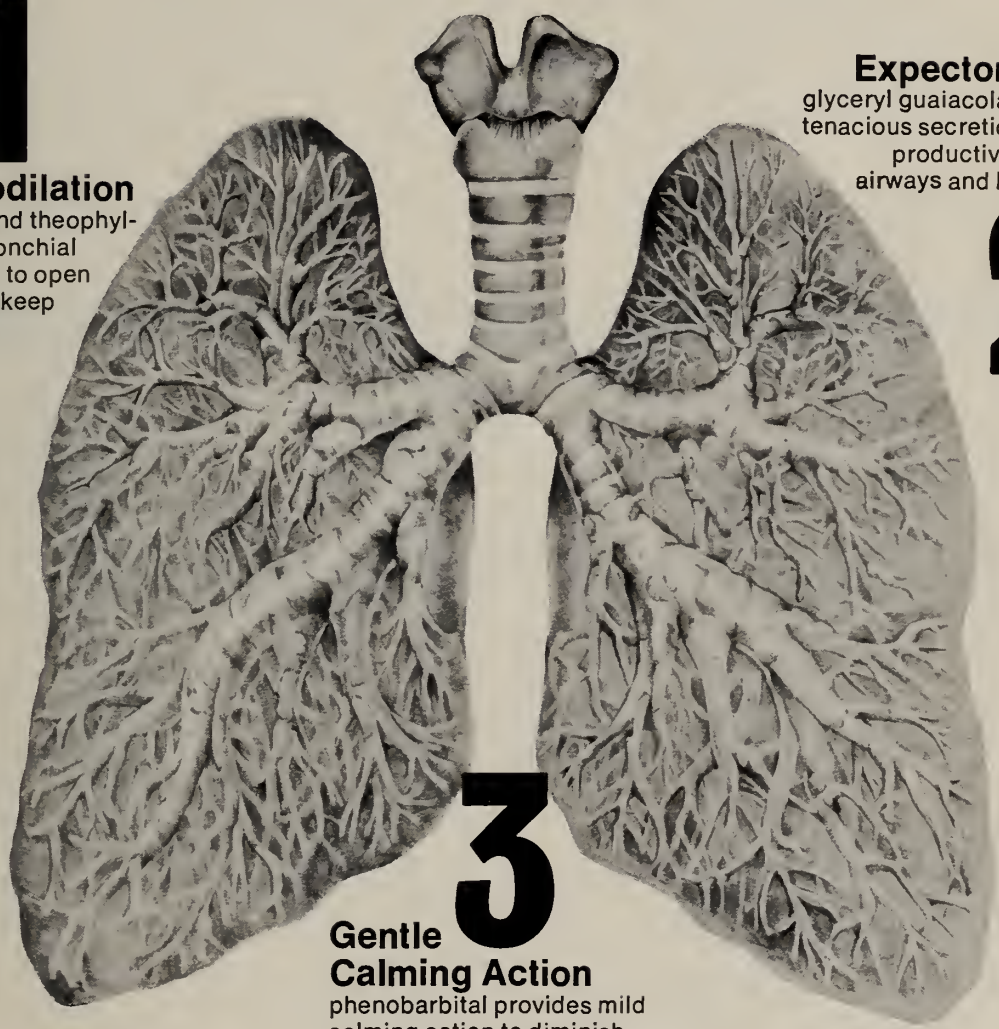

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phenobarbital provides mild calming action to diminish hyperreactions that can trigger bronchospasm.

PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness, or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

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CALIFORNIA
MEDICAL ASSOCIATION

104th Annual Session
AND
Western Scientific Assembly

February 21-26, 1975 • Los Angeles Convention Center • The Biltmore Hotel, Los Angeles

Registration Opens Friday, February 21, 7:45 a.m. at the Convention Center

(A booth will be open at the hotel from Saturday through Tuesday)

SCIENTIFIC SESSIONS	**Begin Friday Morning, February 21** **Conclude Monday, February 24** **Los Angeles Convention Center**	**HOUSE OF DELEGATES**	**Opening Session Saturday, February 22** **Closing Session Wednesday, February 26** **The Biltmore Hotel**

APPLICATION FOR HOTEL ACCOMMODATIONS

Fill in the form below **completely** for room accommodations at the CMA's 1975 Annual Session.

Your reservation request should include the definite date and hour of your arrival and departure.

All reservations, except for suites, must be made through The Biltmore Hotel, 515 South Olive Street, Los Angeles 90013 **by January 21, 1975.**

All SUITE reservations must be cleared through the CMA Convention Office, San Francisco. If you are requesting a suite, direct your requests to: CMA Convention Office, 731 Market Street, San Francisco 94103.

Cancellations: Please notify The Biltmore Hotel of all cancellations.

Changes: All other changes are also to be made directly with the hotel at all times.

THE BILTMORE HOTEL

Singles	$18-22
Twins or doubles	$22-30
Additional person in room	$ 4
1 Bedroom suites	$55 and up

Send to: The Biltmore Hotel, Attn: Reservations
515 South Olive Street, Los Angeles 90013

Please reserve the following accommodations for the CMA's 1975 Annual Session:

Please Indicate Preference:

Single Bedroom $_____ Twin-Bed $_____ Double Bed $_____ Suite $_____

Arrival (date) _____ Hour _____ a.m. p.m. Departure (date) _____ Hour _____ a.m. p.m.

The name and address of each hotel guest must be listed. Include names and addresses of **each** person in a double or twin-bedded room, and names and addresses of **all other persons** for whom you are requesting reservations.

Your Name _____

Address _____ County _____

City and State _____ Zip Code _____

GUESTS' NAMES AND ADDRESSES:

_____

_____

_____

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

ALCOHOL AND DRUG ABUSE

February 13—**Alcohol and Drugs.** USC. Thursday.

CANCER

January 22—**Carcinoma of the Oral Cavity—Second Annual Central Valley Medical Conference.** American Cancer Society at Holiday Inn, Modesto. Wednesday. Contact Dr. Fredrick Mantz, P.O. Box 285, Modesto 95353. (209) 522-5238.

February 28—**Cancer of the Head and Neck.** American Cancer Society, Kern County Unit, at Bakersfield Inn, Bakersfield. Friday. 7 hrs. $25. Contact: Donald C-S Tan, MD and/or Phillip Mahans, DDS, Co-Chairmen, 238 18th St., Bakersfield 93301. (805) 325-5117.

February 28-March 2—**Seminar on Modern Concepts in Oncology—3rd Annual.** UCLA. Friday-Sunday.

Continuously—**Tumor Conference.** Cruden Education Center, St. John's Hospital, Oxnard. Fridays, 12:00 noon-1:00 p.m. Advice and consultation from specialists in surgical, medical, radiotherapeutic, chemotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Cancer program has 3 year accreditation from American College of Surgeons. Contact: D. Gordon Johnston, MD, Dir. of Med. Ed., St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 266.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists (UCLA faculty members) in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John R. Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

December 15—**Advances in Diagnosis and Treatment in Clinical Medicine.** UCLA and Granada Community Hospital at Calif. State Univ., Northridge. Sunday. Contact: Rose Degraffenreid, Granada Community Hospital, 10445 Balboa Blvd., Granada Hills 91344. (213) 360-1021, ext. 730.

January 8—**Pediatric Dermatology.** See Pediatrics, January 8.

January 8-March 26—**Professional Advancement in Cardiological Techniques: Refresher Course in Electrocardiology.** UCLA at Harbor General Hospital, Torrance. Wednesdays, 7-10 p.m. $78.

January 16-18—**The Respective Roles of Medicine and Surgical Treatment in Cardiac Disease in the Adult.** American College of Physicians, UCLA, Cedar-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Thursday-Saturday. $100 for ACP members; $150, non-members. Contact: Registrar, Postgraduate Courses, 4200 Pine St., Philadelphia, Pa. 19104. (215) 222-8120.

January 17-18—**Colonoscopy.** American and Southern Calif. Societies for Gastrointestinal Endoscopy at Beverly Hilton Hotel, Bevery Hills. Friday-Saturday. 9 hrs. $65 for members; $90, non-members. Contact: Melvin Schapiro, MD, 5400 Balboa Blvd., No. 202, Encino 91316. (213) 981-1300.

January 24-25—**Medical Application of Behavior Modification.** See Psychiatry, January 24-25.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

January 26-February 1—**Skiers' Symposium: Pre-, Intra- and Post-Operative Management of the Surgical Patient.** See Of Interest To All, January 26-February 1.

January 29—**Pediatric Dermatology.** See Pediatrics, January 29.

January 29-31—**Pediatric Dermatology.** See Pediatrics, January 29-31.

February 5—**Cardiac Diagnostic Techniques.** Charles R. Drew Postgraduate Medical School at Martin Luther King, Jr., General Hospital, Los Angeles. Wednesday. Contact: Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

February 7—**Stomatology.** STAN. Friday.

February 10-14—**Infectious Disease.** STAN and American College of Physicians at Squaw Valley. Monday-Friday.

February 12-14—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

February 15-19—**American Academy of Allergy.** Town and Country Hotel, San Diego. Saturday-Wednesday. Contact: Janice Manke, AAA, 225 E. Michigan St., Milwaukee, Wis. 53202. (415) 272-6071.

February 19—**Cardiopulmonary Resuscitation.** Charles R. Drew Postgraduate Medical School at Martin Luther King, Jr., General Hospital, Los Angeles. Wednesday. Contact: Office of Continuing Education, Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

February 26-28—**Acute Respiratory Care.** California Thoracic Society at Beverly Hilton Hotel, Beverly Hills. Wednesday-Friday. 21 hrs. $135 for CTS members; $160, others. Contact: Mrs. Laurie Harkess, Prog. Asst., CTS, 224 Pendleton Way, Oakland 94621. (415) 636-1756.

February 27-28—**Endocrinology.** USC at Good Samaritan Hospital, Los Angeles. Thursday-Friday.

February 27-28—**Dermatology for Internists and GPs.** UCSF. Thursday-Friday.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Cardiology Conferences.** Samuel Merritt Hospital, Oakland. First and third Mondays, 12:00 noon-1:30 p.m., Classroom No. 9. Reviews and case discussions on selected topics of current interest in cardiology. Luncheon served. Contact: Thomas P. Forde, MD, 3326 Webster St., Oakland 94609.

Continuously—**Cardiology Conference/General Medical Conference.** Cruden Education Center, St. John's Hospital, Oxnard. Tuesdays, 12:00 noon-1:00 p.m. Conferences including case presentations, discussions of specific cardiology and medical problems. Contact: R. E. Liguori, MD, Dir. of Cardiovascular Laboratory, St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 256.

Continuously—**Cardiology Conferences.** San Diego County Heart Association at Sharp Hospital, San Diego. Fridays, 8-10 a.m. Contact: William Kuzman, MD, Sharp Hospital, 7901 Frost St., San Diego. (714) 277-6121. Or Mrs. Cathy Ware, SDCHA, P.O. Box 3625, San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 294-5663. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conference.** Thursdays, 8:00 p.m. **Cardiosurgical Conference.** Fridays, 2:00 p.m. UCSD at University Hospital, San Diego.

Continuously—**Medical Mortality Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Fridays, 11:30 a.m.

Continuously—**Medical Chest Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

Continuously—**Medical-Surgical G.I. Conference.** UCSD at University Hospital, 3rd floor, rm 3, San Diego. Tuesdays, 12:30 p.m.

Continuously—**Hematology Pathology/Hematology Morphology Conference.** Mondays, 11:00 a.m. **Hematology Clinical Conference.** Mondays, 12 noon. UCSD alternating between University and VA Hospitals, San Diego.

Continuously—**Gastroenterology Conference.** Tuesdays, 11:00 a.m. **Gastrointestinal Conference.** Tuesdays, 12:30 p.m. **Gastroenterology-Pathology Conference.** Wednesdays, 11:00 a.m. UCSD at University Hospital, San Diego.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Preceptorships in Cardiology.** PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Continuously—**Preceptorships in Practical Office Dermatology.** PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Continuously—**Preceptorships in Infectious Disease.** PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Renal Conference.** UCSD alternating between University and VA Hospitals, San Diego. Thursdays, 12:30 p.m.

Continuously—**Rheumatology Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. 2nd and 4th Fridays, 12:30 p.m.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of every other month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detec-

tion and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1534.

Continuously—**Training for Physicians in General Internal Medicine.** LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Dermatology. 11:00 a.m. VA Hospital, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

8:30 a.m., Auditorium, Brown Bldg., Mt. Sinai Hospital, Los Angeles. UCLA.

Dermatology. 10:00 a.m. University Hospital, San Diego. UCSD.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:00 noon. Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., VA Hospital, San Diego. UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:00-10:00 a.m., 4th Floor, UCLA Medical Center. UCLA.

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30-10:00 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

January 17-18—**Colposcopy.** Charles R. Drew Postgraduate Medical School at Airport Hyatt House (17) and Martin Luther King, Jr., General Hospital (18), Los Angeles. Friday-Saturday. Contact: Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

January 27-28—**Neonatal Respiratory Symposium.** USC at Marriott Hotel, Los Angeles. Monday-Tuesday. Will reconvene in Aspen, Colo., January 29-31. Contact: John S. McDonald, MD, Dir., Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054.

January 27-30—**Perinatal Medicine.** USC at Kona Surf Hotel, Kona, Hawaii. Monday-Thursday. $180.

February 8-9—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical & Gynecological Society at Beverly Hilton Hotel, Los Angeles. Saturday-Sunday. $40 for physicians; $15, residents. Contact: Miss Dee Davis, Exec. Sec., 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

February 10-12—**The Heart, Lungs and Circulation in the Fetus and Newborn.** UCSF at Union Square Hyatt Hotel, San Francisco. Monday-Wednesday.

Continuously—**Ob-Gyn Case Review.** Saturdays, 8:00 a.m. **Gyn Tumor Conference/Mortality Conference.** Wednesdays, 12:30 p.m. **Ob-Gyn Pathology Conference.** Wednesdays, 4:00 p.m. UCSD at University Hospital, San Diego.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

8:00-9:00 a.m., Fourth Floor Auditorium, UCLA Medical Center. UCLA.

5:00 p.m. Pickard Auditorium, University Hospital, San Diego. UCSD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

PEDIATRICS

January 8—**Pediatric Dermatology.** USC at Womens Hospital, Los Angeles. Wednesday.

January 14-15—**Adolescent Medicine.** USC. Tuesday-Wednesday.

January 24-26—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 24-26.

January 29—**Pediatric Dermatology.** USC at Womens Hospital, Los Angeles. Wednesday.

January 29-31—**Pediatric Dermatology.** STAN and American Academy of Pediatrics at Holiday Inn, Palo Alto. Wednesday-Friday.

January 30—**The Battered Child.** USC at Casa Royal, Bakersfield. Thursday.

January 30—**Parmelee Memorial Lecture—14th Annual.** Los Angeles Pediatric Society; American Academy of Pediatrics, California Chapter 2, at Los Angeles County Medical Association, Los Angeles. Thursday. Contact: L.A. Pediatric Society, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

February 10-12—**The Heart, Lungs and Circulation in the Fetus and Newborn.** See Ob-Gyn, February 10-12.

Continuously—**Fellowship in Cleft Palate.** See Surgery, Continuously.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD. Small Conference Room, University Hospital, San Diego. Fridays, 12:30 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., and Fridays, 9:30-11:00 a.m., Conference Room 3. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Fourth Thursday of each month, 2:00 p.m., Main Doheny Conference Room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Continuously—**Pediatric Immunology and Allergy Seminar.** UCSD. Wednesdays, 8:00 a.m.

Continuously—**Pediatric Neurology.** UCSD at University Hospital, 3rd floor, rm. 3, San Diego. 1st and 3rd Wednesdays, 12:30 p.m.

(Continued on Page 28)

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing withc prescription.
Description. Proloid (thyroglobulin) is obtain from a purified extract of frozen hog thyroi It contains the known calorigenically acti components, Sodium Levothyroxine (T_4) ar Sodium Liothyronine (T_3). Proloid (thyroglob lin) conforms to the primary USP specificatio for desiccated thyroid—for iodine based c chemical assay—and is also biologicaliy a sayed and standardized in animals.
Chromatographic analysis to standardize th Sodium Levothyroxine and Sodium Liothyr nine content of Proloid (thyroglobulin) is ro tinely employed.
The ratio of T_4 and T_3 in Proloid (thyroglo ulin is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when store at usual room temperature.
Indications. Proloid (thyroglobulin) is thyro replacement therapy for conditions of inade quate endogenous thyroid production: e.g cretinism and myxedema. Replacement therap will be effective only in manifestations of hypo thyroidism.
In simple (nontoxic) goiter, Proloid (thyro globulin) may be tried therapeutically, in nor emergency situations, in an attempt to reduc the size of such goiters.
Contraindication. Thyroid preparations ar contraindicated in the presence of uncorrecte adrenal insufficiency.
Warnings. Thyroglobulin should not be use in the presence of cardiovascular disease un less thyroid-replacement therapy is clearly in dicated. If the latter exists, low doses shoul be instituted beginning at 0.5 to 1.0 grain (3 to 64 mg) and increased by the same amoun in increments at two-week intervals. This de mands careful clinical judgment.
Morphologic hypogonadism and nephrose should be ruled out before the drug is admin istered. If hypopituitarism is present, the adre nal deficiency must be corrected prior t starting the drug.
Myxedematous patients are very sensitive t thyroid and dosage should be started at a ver low level and increased gradually.
Precaution. As with all thyroid preparation this drug will alter results of thyroid functior tests.
Adverse Reactions. Overdosage or too rapic increase in dosage may result in signs anc symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.
Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, T_3 ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.
Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.
(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)
How Supplied. ¼ grain; ½ grain; scored 1 grain; 1½ grain; scored 2 grain; 3 grain; and scored 5 grain tablets, in bottles of 100 and 1000.
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All of which adds up to this: the potency of Proloid is constant...for more consistent results.

PROLOID®
(thyroglobulin)

natural thyroid therapy that leaves nothing to chance

(Continued from Page 26)

Continuously—**Pediatric-Radiology-Urology Conference.** UCSD at University Hospital, Radiology Conference Room, San Diego. 1st and 3rd Fridays, 4:00 p.m.

Grand Rounds—Pediatrics

Tuesdays

Pediatric Cardiology. 7:30 a.m. University Hospital, San Diego. UCSD.

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Pediatric Infectious Disease. 1:30 p.m. University Hospital, San Diego. UCSD.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:30 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., 5th floor Ward, St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

January 15-April 2—**Advanced Psychotherapeutic Techniques—A Practical Approach to Therapy.** UCLA. Wednesday evenings; 12 sessions.

January 24-25—**Medical Application of Behavior Modification.** PMC. Friday-Saturday.

January 25-26—**Autism: Diagnosis, Current Research and Management.** UCLA. Saturday-Sunday.

February 2-7—**Midwinter Program for Psychiatrists.** UCD at Squaw Valley Lodge, Squaw Valley. Sunday-Friday.

Continuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Seminar in Ambulatory Methods.** UCSD at Mental Health Clinic, San Diego. Mondays, 11:00 a.m.

Continuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

Grand Rounds—Psychiatry

Tuesdays

8:30 a.m. VA Hospital, Rm. 2010, San Diego. UCSD.

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

RADIOLOGY AND PATHOLOGY

January 6-7—**The Hemoglobinopathies—Their Manifestations and Laboratory Diagnosis.** Memorial Hospital Medical Center of Long Beach-UCI Center for Health Education and Am. Soc. of Clinical Pathologists. Monday-Tuesday. $140. Contact: Exec. Sec., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

January 8-March 26—**Professional Advancement in Cardiological Techniques: Refresher Course in Electrocardiology.** See Medicine, January 8-March 26.

January 26-28—**Genitourinary Pathology.** UCI at Memorial Hospital Medical Center, Long Beach. Sunday-Tuesday.

January 31-February 2—**Los Angeles Midwinter Radiological Conference—27th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: James F. Mack, MD, St. Mary's Hospital, 509 E. 10th St., Long Beach 90813.

February 5—**Cardiac Diagnostic Techniques.** See Medicine, February 5.

February 5-7—**1975 San Diego Biomedical Symposium.** UCSD at Hilton Inn, Mission Bay, San Diego. Wednesday-Friday. Contact: Dr. Lowell Rosen, Prog. Chr., Dept. of Radiology, UCSD, Box 109, La Jolla 92037. (714) 453-2000, ext. 2268.

February 15—**Abnormal Lab Data: Hypertension.** PMC. Saturday.

February 15-16—**Diagnostic Nuclear Imaging: A Review and What's New.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

February 17-21—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

February 22-23—**A Practical Course in Ultra Sound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

Continuously—**Nuclear Medicine Conference.** Radiology Classroom, St. John's Hospital, Oxnard. Mondays, 12:00 noon-1:00 p.m. Cases reviewed and discussed. Advice and consultation from specialists in the practice of nuclear medicine techniques. Contact: Michael Lopiano, MD, Dir. of Nuclear Med. Dept., St. John's Hospital, 333 N. "F" St., Oxnard 93030. (805) 483-1141, ext. 297.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward I. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Continuously—**Medical X-Ray Conference.** Monday-Friday, 9:30 a.m. (Wednesdays, 8:30 a.m.). **Diagnostic X-Ray Review.** Wednesdays, 3:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Radiology/Pathology Conference.** UCSD at University Hospital, Pickard Amphitheatre, San Diego. Thursdays, 12:30 p.m.

Continuously—**G.I. Radiology Conference.** Fridays, 1:00 p.m. **Pediatric Radiology Conference.** Thursdays, 4:30 p.m. UCSD at University Hospital, San Diego.

Continuously—**Neuroradiology Conference.** UCSD at University Hospital, San Diego, Tuesdays, 4:30 p.m. and at VA Hospital, San Diego, Wednesdays, 2:00 p.m.

Continuously—**Ortho-Radiology Conference.** UCSD at VA Hospital, San Diego. Fridays, 8:00 a.m.

Continuously—**Radiology-Urology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 3:30 p.m.

Continuously—**Pathology Review.** Wednesdays, 9:30 a.m. **Cardiovascular Pathology Conference.** Tuesdays, 8:00 a.m. **Pathology-Urology Conference.** Alternate Mondays, 4:30 p.m. UCSD at University Hospital, San Diego.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

January 6-10—**Anesthesiology 1975.** Anesthesiology Education Foundation and Calif. Soc. of Anesthesiologists at Mammoth Mountain Inn, Mammoth Lakes. Monday-Friday. $175. Contact: Richard W. Patterson, MD, Dept. of Anesthesiology, UCLA. (213) 825-5021.

January 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

January 13-17—**Intensive Course in Otologic Surgery.** Ear Research Institute, USC, St. Vincent's Hospital at Ear Research Institute, Los Angeles. Monday-Friday. $500; $200 for residents. Contact: Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

January 16-18—**The Respective Roles of Medical and Surgical Treatment in Cardiac Disease in the Adult.** See Medicine, January 16-18.

January 17-18—**Colonoscopy.** See Medicine, January 17-18.

January 19—**Orthopaedic Surgery and Surgical Anatomy of the Wrist and Hand.** International College of Surgeons, U.S. Section, at Los Angeles Orthopaedic Hospital, Los Angeles. Sunday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

January 20-23—**Midwinter Clinical Convention for Ophthalmology and Otolaryngology.** The Research Study Club of Los Angeles, Inc., at Hilton Hotel, Los Angeles. Monday-Thursday. 28 hrs. Contact: Russell M. Decker, MD, P.O. Box 49412, Los Angeles 90049.

January 24-26—**Pediatric Anesthesiology—13th Clinical Conference.** Children's Hospital of Los Angeles at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $100. Contact: Wayne Herbert, MD, Division of Anesthesiology, Children's Hospital, P.O. Box 54700, L.A. 90054.

January 26-28—**Refresher Course in Urology.** UCI at Center for Health Education, Long Beach. Sunday-Tuesday. Contact: Chuck Paul, UCI, Dept. UNEX, Irvine 92664. (714) 833-5193.

January 26-February 1—**Skiers' Symposium: Pre-, Intra- and Post-Operative Management of the Surgical Patient.** See Of Interest To All, January 26-February 1.

January 29-31—**Advances in Neurology.** UCSF. Wednesday-Friday.

February 1—**Symposium on Acutely Injured Patient.** International College of Surgeons, So. Calif. Division, at Hollywood Presbyterian Medical Center. Saturday. Contact: M. Hadi Salem, MD, 136 N. Brighton, Burbank 91506. (213) 846-0669.

February 2-5—**Theodor Billroth Course in Surgical Anatomy—16th Annual.** LLU. Sunday-Wednesday.

February 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

February 15—**Sports Injuries to the Knee.** Charles R. Drew Postgraduate Medical School at Martin Luther King, Jr., General Hospital, Los Angeles. Saturday. Contact: Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 564-5911, ext. 391.

February 15—**Surgical Anatomy and Surgery of the Neck.** International College of Surgeons, U.S. Section, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Irving Rehman, PhD, Chr., Postgraduate & Ongoing Education Committee, 5153 Tampa Ave., Tarzana 91356. (213) 344-3305.

February 15-21—**Pan-Pacific Surgical Association—13th Congress.** Hilton Hawaiian Village Hotel, Honolulu. Saturday-Friday. 22½ hrs. Contact: Robert A. Rose, MD, Sec. Gen., Pan-Pacific Surgical Assn., 236 Alexander Young Building, Honolulu 96817. (808) 536-4911.

February 19—**Cardiopulmonary Resuscitation.** See Medicine, February 19.

February 19-21—**Critical Care Medicine and Circulatory Shock.** See Of Interest to All, February 19-21.

February 23-March 7—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

February 26-28—**Acute Respiratory Care.** See Medicine, February 26-28.

February 27-March 1—**American Society for Surgery of the Hand—Annual Meeting.** Fairmont Hotel, San Francisco. Thursday-Saturday. $50. Contact: John A. Boswick, Jr., MD, 4200 E. 9th Ave., #2414, Denver 80220. (303) 394-8549.

February 28-March 2—**Harry Benjamin 4th International Conference on Gender Identity.** STAN. Friday-Sunday.

Continuously—**Fellowship in Cleft Palate.** Rancho Los Amigos Hospital, Downey. One-year fellowship in the total evaluation and management of cleft lip and cleft palate patients. Contact: Libby Wilson, MD, Rancho Los Amigos Hosp., 7601 E. Imperial Highway, Downey 90242. (213) 922-7454.

Continuously—**Anesthesia Lecture Series.** UCSD at University Hospital, 3rd floor conference room, San Diego. Wednesdays, 4:45 p.m.

Continuously—**Anesthesiology Mortality and Morbidity Conference.** UCSD at VA Hospital, Rm. 6006, San Diego. Thursdays, 4:30 p.m.

Continuously—**Neurological Sciences.** St. Francis Hospital, Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens of current material and review of current topics in specialty. Weekly notification of cases available. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital, 3630 Imperial Highway, Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Science Lecture Series.** Dept. of Surgery, St. Mary's Hospital, San Francisco. Mondays, 11:15 a.m.-12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Postgraduate traineeships of 4-14 days duration, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at St. Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser San Francisco, and Harkness Memorial Hospitals. Third Tuesday of each month, 6:00 p.m. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at Los Angeles County-USC Medical Center. Mondays, 7:00-9:00 p.m. Contact: Dept. of Orthopedics, USC School of Med., 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arrangement.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, San Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Classroom. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Mortality and Morbidity Conference.** UCSD alternating between University and VA Hospitals, San Diego. Saturdays. 9:30 a.m.

Continuously—**Ortho Surgical Conference.** UCSD at University Hospital, 3rd floor conference room, San Diego. Wednesdays, 8:00 a.m.

Continuously—**Otolaryngology Conference.** UCSD alternating between University and VA Hospitals, San Diego. Fridays, 8:30 a.m.

Continuously—**Laryngeal Physiology.** UCSD at VA Hospital, San Diego. Fridays, 8:30 a.m.

Continuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Trauma Conference.** UCSD at University Hospital, 1st floor conference room, San Diego. Tuesdays, 3:30 p.m.

Continuously—**Vascular Surgery Conference.** UCSD alternating between VA and University Hospitals, San Diego. Thursdays, 4:00 p.m.

Continuously—**Radiology-Urology Conference. Pathology-Urology Conference.** See Radiology and Pathology, Continuously.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Lebanon Hall Auditorium, Cedars-Sinai Hospital, Los Angeles. UCLA.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery**. 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Otolaryngology. 12:00 noon. University and VA Hospitals, San Diego. UCSD.

Neurology, Neuropathology, Neurosurgery. 4:00 p.m. University and VA Hospitals, San Diego. UCSD.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital, 1st, 3rd, 5th Sat.; VA Hospital, 2nd, 4th Sat., San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

Orthopedic Surgery. 8:00-9:00 a.m. UCSF. September 21-June 14, 1975. Subjects to be announced.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

December 27-28—**Symposium on Innovations in Athletic Conditioning and Sports Medicine—2nd Annual.** University Extension at UC, Berkeley. Friday-Saturday. 15 hrs. $50. Contact: Nathan W. Cohen, PhD, Dir., Curriculum Development in Science, UC Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1061.

January 9-10—**New and Old Antibiotics.** USC. Thursday-Friday.

January 14-April 22—**Acupuncture for Management of Musculo-Skeletal Pain.** UCLA. Mondays, 7-10 p.m.

January 23-24—**Environmental Health and Safety in Health Care Facilties. UCSF.** Thursday-Friday.

January 26-February 1—**Skiers' Symposium: Pre-, Intra- and Post-Operative Management of the Surgical Patient.** Bernard Levinson, MD, Carmichael, Symposium Coordinator. Snowbird-Alta, Utah. Sunday-Saturday. Contact: Daman-Nelson Travel Agency, 115 Mission St., San Francisco. (415) 434-2018.

January 27-31—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 29-February 1—**Physician and the Hospital.** USC at Ahwahnee Hotel, Yosemite. Wednesday-Saturday.

February 1—**Symposium on Acutely Injured Patient.** See Surgery, February 1.

February 3-8—**Family Practice Refresher Course—6th Annual.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 5-7—**Physicians in Family Practice—25th Annual Course.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Ms. Ann Raisbeck, Asst. to Dir. of Med. Education, Mt. Zion Hosp. & Med. Center, 1600 Divisadero St., San Francisco 94115. (415) 567-6600.

February 19-21—**Critical Care Medicine and Circulatory Shock.** USC at Anaheim Convention Center, Anaheim. Wednesday-Friday.

February 21-22—**The Process and Treatment of Aging.** Vista Hill Foundation at Hilton Inn, San Diego. Friday-Saturday. $35; $20 for students and interns. Contact: Keith S. Ditman, MD, Vista Hill Foundation, 7798 Starling Dr., Suite 206, San Diego 92123. (714) 278-6761.

February 21-22—**Emergency Care.** UCD at Sahara Club, So. Lake Tahoe. Friday-Saturday.

February 21-26—**California Medical Association—104th Annual Session.** Los Angeles Convention Center. Friday-Wednesday.

February 27-28—**Dermatology for Internists and GPs.** See Medicine, February 27-28.

February 28-March 2—**Harry Benjamin 4th International Conference on Gender Identity.** See Surgery, February 28-March 2.

Continuously—**Psychiatric Seminars for Physicians.** San Francisco Psychoanalytic Institute, San Francisco. 1st and 3rd Thursdays, October-May, 1975; 8:00 p.m. Invitations to all non-psychiatric physicians of 9 Bay Area counties. Contact: Jerome D. Oremland, MD, Chr., Extension Division, S. F. Psychoanalytic Institute, 2420 Sutter St., San Francisco 94115. (415) 931-4205.

Continuously—**Bedside Clinics.** USC. September 26-December 19. Thursdays, 7:30-9:30 p.m.

Continuously—**Clinical Conferences.** UCSF at Community Hospital, Santa Cruz. October 9, 1974-June 11, 1975. Wednesdays.

Continuously—**Continuing Medical Education Noon Conferences.** The Hospital of the Good Samaritan, Los Angeles. Every weekday, 12-1 p.m. For monthly calendar, contact: Janie Sternal, Coord., Cont. Med. Ed., Hosp. of the Good Samaritan, 1212 Shatto St., Los Angeles 90029. (213) 482-8111.

Continuously—**Emergency Room Lecture Series.** UCSD at University Hospital, San Diego. Wednesdays, 10:00 a.m.

Continuously—**Endocrinology, Metabolism, Reproductive Medicine, Genetics Conference.** UCSD alternating between University and VA Hospitals, San Diego. Wednesdays, 11:30 a.m.

Continuously—**Preceptorships in International Health, Microbiology, Pharmacology and Experimental Therapeutics, Physiology and Basic Sciences.** UCSF. By special arrangement.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; La Palma Intercommunity Hosp., La Palma; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Riviera Hosp., Torrance; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $15 per session. Contact: William J. Newman, MD, 280 Perkins St., Sonoma 95476. (707) 996-2165.

Continuously—**Basic Science Seminar.** UCSD Wednesdays, 9:15 a.m., University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

Continuously—**Medical Media Network.** Programs and study guides produced in association with faculties of major medical schools and centers throughout the U.S. MMN administered by University Extension, UCLA. Rental or purchase, 16 mm, super 8 mm, videotape and video-cassette. Provides physicians with current educational programs. Contact: Ms. Jan MacAllister, Distribution Mgr., MMN, 10995 Le Conte Ave., Room 540, Los Angeles 90024. (213) 825-7781.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Providence Hospital, Providence Hall Auditorium, 700 N.E. 47th Avenue, Portland 97213:

December 11—7:00 p.m.—**Blue Cross as a Consumer Advocate**

December 17—7:00 p.m.—**Newer Approaches to the Treatment of Leukemia**

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

CARDIOLOGY

June 5-7—**Progress in Coronary Artery Disease and Valvular Heart Disease,** Portland. Contact: S. H. Rahimtoola, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland, 97201.

FAMILY PRACTICE

February 9—**Practical Genetics for the Family Physician,** 9:00 a.m. to 5:00 p.m., Hilton Hotel, Portland. Contact: Neil Buist, MD, 429 S.W. Fourth Ave., Portland, 97204.

February 10-14—**General Family Practice Review,** Hilton Hotel, Portland. Contact: William Fisher, MD, University of Oregon Medical School, Department of Family Practice, 3181 S.W. Sam Jackson Park Road, Portland, 97201.

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds,** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

January 16-17—**What's New in Pediatrics '75.** Thursday-Friday. Seattle. Fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, 98195. (206) 543-1050.

January 22-24—**Advances in Neurology.** Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 18 hrs. $100, ACP members; $150, non-members; $50, ACP Associates. Contact: M. H. Jackson, Registrar, Postgraduate Courses, American College of Physicians, 4200 Pine St., Philadelphia, Pa., 19104.

January 24-25—**Tax, Estate and Financial Planning for Physicians.** Friday-Saturday. Seattle. $75. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

January 26-February 1—**Advances in Perinatology.** Sunday-Saturday. Sun Valley, Idaho. 37½ hrs. $100 for physicians, $30 for nurses and other health professionals. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 7-8—**A Modern Approach to Allergy.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

February 19-20 — **Trauma-Burns-Shock: Emergency Medical Care—Univ. of Washington School of Medicine's Western Circuit Course.** Longview, Wash., Feb. 19; Olympia, Wash., Feb. 20. 4 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 20-21—**Thirteenth Annual Symposium on Respiratory Disease.** Thursday-Friday. Olympic Hotel, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 28-March 1—**The Intensive Care Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

March 4-5—**Trauma-Burns-Shock: Emergency Medical Care—Univ. of Washington School of Medicine's Western Circuit Course.** Bremerton, Wash., Mar. 4; Bellingham, Wash., Mar. 5. 4 hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 14-15—**Current Concepts in Cardiology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

March 17-21—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $250. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, S-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 20-21—**Basic Sciences for Clinicians.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 31-April 4—**Advances in Family Practice.** Monday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 40 hrs. $100. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 4-5—**Acid Base and Blood Gas Management in the Surgical Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA 3-3700, Ext. 470.

April 10-11—**Developmental Disabilities: Early Identification and Intervention Can Make a Difference.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee not set. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 24-25—**Conference on Respiratory Care.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours not set. $75. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

Bio-Science Laboratories
Laboratory 5

Boehringer Ingelheim Ltd.
Catapres 10, 11

Breon Laboratories, Inc.
Bronkotabs 21

Burroughs Welcome Co.
Empirin Compound with Codeine 11
Neosporin Ointment 19

Classified 20, 34

CMA-104th Annual Session and Western Scientific Assembly
Hotel Accommodations 22

Compton Foundation 20

Dairy Council of California 13

Dorsey Laboratories
Triaminic Syrup 4
Triaminic Expectorant Plain 17

Eli Lilly & Company
Kefzol 18

Merck Sharp & Dohme
Triavil 14, 15, 16

Pharmaceutical Manufacturers Association
Prescription Ads 6, 7

Roche Laboratories
Librium ..... 2nd Cover and Page 1

Security Pacific Bank ..... 12 and 3rd Cover

State Compensation Insurance Fund ..... 4th Cover

Warner-Chilcott Laboratories
Proloid 26, 27

Wells Fargo Bank 3

Wyeth Laboratories
Bicillin/Wycillin 8, 9

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ABDOMINAL OPERATIONS—Sixth Edition—Volumes 1 and 2—Rodney Maingot, FRCS, and British and American Contributors. Appleton-Century-Crofts, A Publishing Division of Prentice-Hall, Inc., Publishers, Englewood Cliffs, NJ (07632), 1974. 2,240 pages, $82.50.

ALCOHOL AS A DRUG—A Curriculum on Pharmacology, Neurology and Toxicology—Charles E. Becker, MD. Director, Alcohol Detoxification Unit, San Francisco General Hospital, and Assistant Professor of Medicine in Residence, University of California, San Francisco; Robert L. Roe, MD, Director, Drug Detoxification Unit and Chief, Rheumatology Unit, San Francisco General Hospital, and Assistant Professor of Medicine in Residence, University of Calfornia, San Francisco; and Robert A. Scott, MD, Neuologist. Acute Detoxification Unit, San Francisco General Hospital, Assistant Professor of Neurology in Residence, University of California, San Francisco. Medcom, Inc., 2 Hammarskjold Plaza, New York City (10017), 1974. 99 pages, soft cover, $9.95.

AWAKENING—Dr. Oliver W. Sacks, Instructor in Neurology, Albert Einstein College of Medicine. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 249 pages, $7.95.

THE CARE OF THE RHEUMATOID HAND—Third Edition—Adrian E. Flatt, MD, M Chir., Professor of Orthopaedic Surgery, University of Iowa, Iowa City, Hunterian Professor of Royal College of Surgeons of England, Civilian Consultant to U.S. Air Force in Hand Surgery. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis (63103), 1974. 296 pages, $24.75.

CLINICAL CHEMISTRY—PRINCIPLES AND TECHNICS—Second Edition—Richard J. Henry, MD, Vice President, Bio-Science Enterprises, Westwood, Calif.; Donald C. Cannon, MD, PhD, Director, Bio-Science Laboratories, Van Nuys, Calif.; and James W. Winkelman, MD, President, Bio-Science Laboratories, Van Nuys. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Ave., Hagerstown, MD (21740), 1974. 1,641 pages, $37.50.

CREATIVE AGGRESSION—George R. Bach, PhD, Founder and Director, Institute of Group Psychotherapy of Los Angeles; and Herb Goldberg, PhD, Professor of Psychology, California State University, Los Angeles. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 407 pages, $8.95.

DORLAND'S ILLUSTRATED MEDICAL DICTIONARY—Twenty-fifth Edition. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1974. 1,748 pages, 52 plates (23 in full color), $21.50, Standard, $28.50, Deluxe (thumb indexed).

ESSAYS ON LONGEVITY—Samuel Kahn, MD. Philosophical Library Inc., 15 East 40th Street, New York City (10016), 1974. 198 pages, $10.00.

(Continued from Page 20)

PHYSICIANS WANTED

OPPORTUNITY FOR INTERNIST EDUCATOR-CLINICAN (must be Diplomate American Board of Internal Medicine) as training director, Internal Medicine Pathway in a Primary Care Residency Program. Applicant should have experience in the organization and administration of a teaching and patient care program in general internal medicine, including ambulatory care, on either a university campus or at a medical school-affiliated hospital. Interested individuals should write for a detailed job description and send their Curriculum Vitae to Robert H. Crede, MD, Chairman, Division of Ambulatory and Community Medicine, University of California, San Francisco, San Francisco, CA 94143. The University is an Equal Opportunity employer with an Affirmative Action Program.

INTERNIST—Sub-specialty desired but not necessary for growing 19-member multi-specialty partnership. New building adjacent to modern hospital, 30 minutes to San Francisco. Contact S. Oppenheimer, MD, 27212 Calaroga Ave., Hayward, CA 94545.

SITUATIONS WANTED

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Robin Hood handled a lot of money over the course of his career. But he found fortune easier to acquire than to retain. And spent most of his life living on nuts and berries.

He is not a lone example. Many talented, hard working people find it easier to make money than to manage it. Security Pacific Bank's Trust Department enables such people—and their families—to attain their economic goals. No single investor, no matter how sophisticated, could provide the time, research and collective experience that goes into the building of each portfolio.

Professional investment service is not the only benefit our trusts provide. Should you become ill or incapacitated, Security Pacific Bank will continue to manage your portfolio, and at the same time apply income to medical expenses and the needs of your family. Finally, a trust with Security Pacific Bank may enable you to combine tax savings, greater family income and even a gift to your favorite charity.

Mr. Hood would approve of that.

To make an appointment, call any of our over 470 branch offices. There is no cost or obligation.

SECURITY PACIFIC BANK
SOMETHING SPECIAL

1974 SECURITY PACIFIC NATIONAL BANK MEMBER FDIC

Case history #6

Vernon's well-being comes first.

Vernon's being well comes first.

On October 26, 1963, Vernon Bailey was working atop an oil derrick in Bakersfield when he lost his footing and fell 35 feet to the ground, suffering a spinal injury with permanent paraplegia. The hardest years of his life began.

State Compensation Insurance Fund helped the primary physician to transfer Vernon immediately to a Spinal Cord Center, where he was taught the necessary medical techniques and skills of self-care that would enable him to live as full and normal a life as possible.

For the next ten years, State Fund's rehabilitation team worked closely with Vernon and his doctors in helping to rebuild his life.

Today, although Vernon has been unable to return to work, his financial future is secure. Arrangements were made for Vernon to receive a lump-sum payment of his projected lifetime benefits, and State Fund helped him invest the money wisely.

Vernon has come a long way since 1963. His problems aren't over, but he has built himself a future—with the help of State Fund.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND